AD_____

AWARD NUMBER: W81XWH-04-1-0469

TITLE: Advance Care Planning: Experience of Women with Breast Cancer

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REPORT DATE: July 2006

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
                      Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
                                      Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
01-07-2006	Final	14 Apr 2004 – 13 Jun 2006

4. TITLE AND SUBTITLE

Advance Care Planning: Experience of Women with Breast Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-04-1-0469

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Michigan State University
East Lansing, Michigan 48824-1046

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Advance care planning (ACP) enables women with breast cancer to proactively document their end-of-life care preferences. The purpose of this study is to describe the prevalence and predictors of ACP documents and the desire for ACP information for women undergoing chemotherapy, and to test the effectiveness of an ACP intervention among women attending breast cancer support groups. Among the 236 women undergoing chemotherapy, 76 women (32%) had ACP documents. Increased probability of having ACP documents was associated with increasing age, being Caucasian, and trust in the oncology health care provider. Among the 80 women recruited from support groups, the ACP intervention was successful in improving ACP knowledge, especially among African-American women. The ACP intervention resulted in 58% (n =46) women completing ACP documents. The results of this study provide unique insights into factors that are associated with ACP during chemotherapy. Results also supported the effectiveness of the ACP intervention among women attending breast cancer support groups. Continued ACP intervention is warranted, especially among African-American women with breast cancer, to improve knowledge and ACP document completion rates. This will further reduce end-of-life health care disparities and promote women's ability to have control over the care they receive at end of life.

15. SUBJECT TERMS
Advance care planning, breast cancer

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	UU	88	**19b. TELEPHONE NUMBER** *(include area code)*
U	U	U			

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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Introduction

Breast cancer is the second leading cause of cancer deaths in women. Documented shortcomings in end-of-life care include deficiencies in provider/patient communication, excess reliance on aggressive treatment, and disparity between the way people die and the way they want to die. Advance care planning (ACP) enables women with breast cancer to proactively document their end-of-life care preferences. The purpose of this study is to describe the prevalence and predictors of ACP documents and the desire for ACP information among women undergoing chemotherapy, and to test the effectiveness of an ACP intervention among women attending breast cancer support groups. The ACP Project integrated into two Randomized Control Trials (RCTs) questions regarding ACP, which allowed for prospective examination of ACP documentation as women with breast cancer proceeded through chemotherapy. It also recruited women with breast cancer from support groups to test the effectiveness of an ACP intervention.

The body of this report will first describe the training activities. It will then review the methods, analysis, and results of the data obtained from the RCTs. Finally, it will detail the modification of recruitment strategies for the ACP pilot intervention project, the methods of the project, and the project's analysis and results.

Body

Training Activities

Research participation: *gain experience/skills in multi-site RCTs.*
(Statement of Work Task II #8)

I participated in selective aspects of the multi-site RCTs: *Family Home Care for Cancer - A Community-Based Model*, Dr. Barbara Given, PI (R01 CA030724); and *Automated Telephone Monitoring for Symptom Management*, Dr. Charles Given, PI (R01 CA079280). These two studies focused on providing symptom management interventions for individuals with solid cancer tumors, including women with breast cancer. From April 2005 to the end of December 2005, the aspects of the RCTs that I was involved in included: quality assurance (QA); meeting participation (coordinator, intervention, and interview meetings); and taped evaluations of the nurses interventions with patients, including providing input into the development of a new tape-evaluation form for nurses.

Learning about QA included reviewing the web tracking system developing a QA plan for determining which questions to program into ACESS each month; these questions needed to establish whether all required fields were being completed by FCRP staff. QA also included meetings with Amy Hoffman, a doctoral candidate in the College of Nursing, mentored by Barbara Given; and with Cindy Espinosa, project manager, to learn how the QA audits were conducted each month.

Under the supervision of Dana Berry-Richardson, Intervener Coordinator, and along with Amy Hoffman, I have reviewed at least 2 intervention tapes monthly, providing timely feedback to the nurses or the non-nurse interventionists. Increasing my involvement with the intervention by going through intervention training myself, and participating in the ongoing evaluation of tapes, provided me both with the skills to learn about and maintain treatment fidelity of intervention delivery during the course of a trial, and the longitudinal experience of watching improvement over time and problem solving in intervention delivery.

Being invited to participate in coordinator, interviewer, and intervention meetings related to the management of the RCTs provided valuable insight into the day-to-day issues that arise and the problem solving that occurs in managing large, multi-site, RCTs. Monthly coordinator meetings covered overall issues related to grant activities. These meetings included discussion of recruitment, attrition, interviewer issues, intervention issues, QA, medical record audits, data management, software and hardware issues, and data analysis. Bimonthly interviewer meetings covered information relevant to interviewers, such as monitoring the tracking system for assignments, sharing issues related to entering data into SNAP (a computer assisted interviewer program in which all data were collected), difficult situations or patients an interviewer had had

in the last two weeks, and the review of policies and protocols. Bimonthly intervention meetings covered issues that the intervention nurses grappled with. These issues included methods of orienting participants to the study; how to deliver the intervention in the most effective manner; maintaining consistency with how nurses documented assessment of interventions, symptoms, and the plan of care in the computer tracking system; and summarizing the goals for the coming week for participants at the end of each contact.

In August 2005, I was invited to attend a data analysis planning meeting. This was a full-day meeting which involved the PIs, consultants, and statisticians of the grants. In this meeting, discussions included baseline equivalencies and the need for adjustments, how to deal with differences in attrition between arms of the studies, analyses of minorities, review and critique of the specific aims, and the planned analyses for the specific aims.

Overall, the participation with selected activities of the RCTs enhanced my methodological expertise in designing and conducting randomized control trial research and data analysis. It also developed my skills in measurement and behavioral intervention methodology, including those specifically targeted at symptom outcomes of women with breast cancer within community settings.

In summary, the activities related to Statement of Work Task I #5 and Statement of Work Task II #8, detailed in the 2005 annual report and above, respectively, were a unique strength of my training. Having the opportunity to be involved, over the last two years, from the beginning of the implementation of two NCI R01 funded, multisite, randomized clinical trials provided in-depth, hands-on cancer research training. These trials and my involvement were overseen by two senior researchers with twenty years each of NIH funding and a wealth of experience with breast and related cancers; my association with the Drs. Charles W. and Barbara Given enabled me to realize my goal of becoming a successful independent nurse breast cancer clinical researcher.

Manuscripts: *Preparation and submission of four manuscripts from* The Family Home Care for Cancer Research Program *(FCRP) data sets*.
(Statement of Work Task I #6 and Task II #9)

Published:

Doorenbos, A. Z., Verbitsky, N., Given, B., & Given, C. W. (2005). An analytic strategy for modeling multiple item responses: A breast cancer symptom example. *Nursing Research, 54,* 229-234.

Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. (2006). Physical functioning: Effect of behavioral intervention for symptoms among individuals with cancer. *Nursing Research, 55,* 161-171.

Accepted:

Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. Symptoms in the last year of life
among individuals with cancer. *Journal of Pain and Symptom Management*.

Revised and Resubmitted:

Doorenbos, A. Z., Given, B., Given, C. W., Wyatt, G., Gift, A., Rahbar, M., & Jeon, S. Impact of
end-of-life care for caregivers of family members with cancer. Submitted to *Research in
Nursing and Health*.

Observations:

Being mentored by senior cancer researchers with over 100 publications and having access
to Drs. Charles W. and Barbara Given's data sets facilitated my ability to develop my manuscript
preparation skills. This skill set included identifying a problem, choosing an appropriate
analytical technique to examine the issue, and presenting the results and discussing their
importance in relation to the current body of scientific knowledge. Having two manuscripts
published in *Nursing Research* is a testament to the success of the manuscript writing mentoring.
Nursing Research is a top-tier nursing journal with a 12% acceptance rate. The *Journal of Pain
and Symptom Management* is the official journal of both the United States Cancer Pain Relief
Committee and the National Hospice and Palliative Care Organization. Having an accepted
manuscript in this journal provides further evidence of my development as an end-of-life cancer
researcher.

Coursework
(Statement of Work Task I #7 and Task II # 7)

(A) Michigan State University, EPI 827: *The Nature and Practice of Scientific Integrity*.
Taught by Dr. Terry May, Adjunct professor, Department of Epidemiology. Spring 2004.

The Nature and Practice of Scientific Integrity stressed the responsible conduct of research
as a component of the process of inquiry. Some of the active discussion in the course covered the
responsible conduct of research; the future of science, including the NIH Director's Panel on
Clinical Research; and examples of misconduct, including historical and institutional lapses,
conflict of interest, and ethical challenges. Increasing my knowledge base regarding the
responsible conduct of research was an essential first step in my training and will continue to
guide my future research.

(B) National Institutes of Health, Summer Institute on Randomized Clinical Trials with
Behavioral Interventions. Summer 2004.

I was selected to participate at the NIH summer institute on RCTs with behavioral interventions. This is a semester course taught by leading experts in RCT using behavioral interventions over two weeks in July at the Arlie conference center. Sessions covered a multitude of topics related to RCT. Ethical and human subject related topics included stopping rules and data safety and monitoring boards. Statistical sessions included discussions related to power analysis and sample size, missing data, adjusting for covariates, mediation, moderation, survival analysis, intent to treat analysis, mixed effects, growth curves and longitudinal models. Other topics included: design; selection of test measurements and instruments; external and internal validity; randomization; control groups and blinding; building leading and maintaining effective research teams; hypothesis specification; treatment implementation; inclusion and exclusion criteria. Benefits of this experience went far beyond active participation in the dyadic lectures offered, as this institute provided networking opportunities with other early-career researchers in the field of cancer research, as well as consultation with leaders in RCT methodology. This NIH summer institute far exceeded the training objective of a normal RCT course.

(C)   Michigan State University, EPI 823: Cancer Epidemiology. Taught by Dr. Ellen Velie, Assistant Professor, Department of Epidemiology. Winter 2005.

This course focuses on cancer surveillance and biology. It reviewed research methods in cancer epidemiology and provided the opportunity to further develop my skills in critically reading and evaluating published cancer epidemiology literature. It facilitated my understanding of various aspects of cancer, types of malignancies, and the biological mechanisms which may impact end-of-life outcomes. It also provided an up-to-date knowledge of important issues in the field of cancer research.

(D)   University of Michigan, ISR 988.220 *Hierarchical Linear Models (HLM).* Taught by Dr. Joop Hox, Professor, Department of Statistics, Utrect University, The Netherlands. Summer 2005.

This course covered multi-level analysis techniques for data that have hierarchical structures. It demonstrated using HLM to look at longitudinal and panel data, growth curve modeling, and meta-analyses. It also covered using HLM for dichotomous data and proportions, ordinal data, multivariate outcomes, and data structures that included crossed as well as nested factors. This course provided knowledge of advanced hierarchical linear models and discourse in multi-method analysis.

(E)   University of Michigan, ISR 988.213 *Web Survey Design.* Taught by Dr. Mick Cooper, Associate Professor, Institute of Social Research. Summer 2005.

This course focused on the design of web survey instruments and procedures moving to analysis. It was based on theories of human-computer interaction and covered interface design. Throughout the course, the latest cutting-edge research on self-administered questionnaires was presented. Additionally, the latest issues in computer-assisted interviewing were also reviewed. This course facilitated by ability to further develop computer-assisted interviews beyond what was used in the current study.

(F)   University of Michigan, Biostats 675 *Statistical Survival Analysis*. Taught by Douglas Schaubel, Assistant Professor of Biostatistics, School of Public Health. Fall 2005.

This course focused on concepts and methods for analyzing survival-time data obtained from following individuals until occurrence of an event or their failure to follow-up. It covered survival-time models, clinical life tables, survival distributions, mathematical and graphical methods for evaluating goodness of fit, comparison of treatment groups, regression models, proportional hazards models, and censoring mechanisms. This course met the objective of learning about design and analysis for longitudinal data.

Short Courses:

(G)   NIH State-of-the-Science Conference on Improving End-of-Life Care. December 2004.

This three-day conference raised key questions regarding what defines the transition to end of life: those outcome variables that are important indicators of the quality of the end-of-life experience for both dying persons and their families. Discussions and presentations also addressed health care system factors associated with end-of-life outcomes, and interventions found to impact end-of-life outcomes. The conference concluded with discussions about the future research directions for improving end-of-life care. This course provided the knowledge of what are the important variables in need of clinical interventions to improve the end-of-life experience of women with breast cancer.

(H)   Michigan Center for Urban African American Aging Research (MCUAAAR) Summer workshop. June 2005.

This three-day intensive NIH-sponsored workshop was presented by top African-American researchers across the nation. The workshop covered recruitment and retention of African-American participants to cancer clinical trials. Discussions included use of both qualitative and quantitative designs and analysis of data using multi-methods. It also covered statistical issues in social and ethnic disparities. Additionally, the workshop provided knowledge regarding developing community research partnerships, perceived racism and health, and racial differences in quality of life. Knowledge gained from this course was immediately applied toward improving minority recruitment and retention.

Seminar and workshop attendance and participation
(Statement of Work Task I #8)

(A)   Behavioral Cooperative Oncology Group (BCOG) of the Walther Cancer Institute

BCOG holds an annual Fall meeting in Indianapolis, Indiana, which I attended both years. At these meetings, interactive discussion of cutting-edge behavioral research is facilitated. BCOG senior scientists—including Dr. C. Given, Dr. B. Given, Dr. L. Northouse, Dr. B. Cimprich, Dr. V. Champion, Dr. S. Rawl, and Dr. C. Skinner—each presented the progress of their research. All attendees were included in interactive discussion of the research.

At the Fall 2004 meeting, our presentation, *Advance Care Planning: Experience of Women with Breast Cancer*, provided the opportunity for interaction with BCOG faculty researchers, focusing specifically on the ongoing DoD sponsored research. BCOG is unique in that it specifically plans for and facilitates interactive discussion by asking pre- and post-doctoral fellows to bring forth questions and concerns regarding their research. Discussion included the most efficacious "teachable moment" in the breast cancer treatment trajectory for discussing ACP, and the best location to access women with breast cancer in order to offer ACP intervention. Being given the floor, within an intellectually nurturing environment, to present our specific concerns and generate discussions with senior cancer researchers was invaluable. This additional mentoring further enhanced my ability to conduct research founded on a multidisciplinary platform that contributes to, and focuses on, individuals with cancer.

(B)   Department of Epidemiology seminar series

I have selectively attended the Department of Epidemiology sponsored biweekly seminar series during the two academic years. Speakers have included Michigan State University faculty members, Michigan Department of Community Health public health professionals, and invited guests from across the US. Dr. Osuch, a member of the mentoring team, is a Professor in the Department of Epidemiology. She provided guidance regarding regional breast cancer support groups to contact. Additionally, with her wealth of clinical experience Dr. Osuch provided valuable insights into treatment variables that may affect ACP among women with breast cancer.

(C)   Michigan State University, Office of the Vice President for Research and Graduate Studies workshops

The MSU Graduate School offered six ethics workshops during the 2004/2005 academic year. The topics of the workshops were (1) the graduate experience, (2) ethical challenges, (3) responsibility for integrity, (4) responsibility to the institution, (5) responsibility to the subject, and (6) responsibility for objectivity.

During the 2005/2006 academic year, I attended *Making the Right Moves: Key Issues for Postdocs and New Faculty*. Four workshops were offered: (1) research planning and proposal

preparation, (2) networking and the need for collaborations, (3) understanding the external peer review process, and (4) managing research and research groups.

An additional workshop series offered by MSU Graduate Studies that I attended was *NIH peer review, grant writing and funding opportunities*. Three workshops were offered in this series: (1) fundamentals of NIH granting process, (2) scientific peer review, and (3) grant writing for success.

(D)   Wayne State University (WSU), End-of-Life Interdisciplinary Project (EOL-IP)

EOL-IP is a national exemplar of a multidisciplinary team with an interest in EOL care. I have been an active member of the project since its inception. Having a continuing relationship with the EOL-IP has provided me with ongoing consultation, directed EOL education, monthly journal club discussions, and advice on the many end-of-life aspects of this research. Dr. Gelfand, past coordinator of the Project represented the project at mentorship team meetings.

Observations:

In summary, seminar attendance detailed in the 2005 annual report and what is detailed above facilitated interaction with local and regional researchers and clinicians active in cancer and end-of-life research. Seminar participation and the mentorship team provided networking and exposure to researchers in epidemiology, economics, nursing, sociology, medicine, surgery, statistics, and communications.

Conference attendance and presentations
(Statement of Work Task I #9, Task II #10, Task III #3)

(A)   Michigan Cancer Consortium. September 2004 and 2005.

The Michigan Cancer Consortium (MCC) is a statewide, broad-based partnership of public and private organizations. The MCC annual meeting is a forum for collaboration to reduce the burden of cancer among residents of Michigan. We developed a poster presentation of our work examining the impact of end-of-life care on caregivers of family members with cancer, which was presented in 2004. In 2005, we were invited to present preliminary results of *Advance Care Planning: Experience of Women with Breast Cancer* in a poster format.

B)   National Congress on the State of the Science in Nursing Research. October 2004.

The purpose of this conference is to create a national forum for communicating emerging scientific discoveries related to nursing practice; to disseminate research findings that can influence practice, education, research and health care policies; and to influence the nursing research agenda of the future. This conference included our presentation of the paper "The

Impact of a Cognitive Behavioral Intervention on Symptom-Based Limitations and Physical Function."

(C)   The Gerontological Society of America Annual Scientific Meeting. November 2004 and 2005.

The Gerontology Society annual meeting provides interaction with an interdisciplinary group, many of whom have end-of-life interests. Membership in the cancer interest group facilitated interactions with a diverse group of researchers interested in cancer and oncology. As the burden of cancer is increasing in the elderly, and elderly cancer patients are more likely to experience mortality and morbidity, the ability to network with researchers with an expertise in gero-oncology enhances my ability to conduct research with this growing segment of the population.

At the 2004 GSA conference, a podium presentation of our paper "Impact of End-of-Life Care for Caregivers of Family Members over 65 with Cancer" was presented. At the 2005 GSA conference, as part of a symposium, the podium presentation "Aging Issues in Cognitive Behavioral Interventions for Symptoms with Cancer Patients" was given.

(D)   8th National Conference on Cancer Nursing Research. February 2005.

The attendees of this conference are the top cancer nursing researchers in the country. The purpose of this conference is to provide a forum for scholarly exchange related to the foundation and advancement of cancer nursing science and its practice. As it is a specifically focused conference, interactions are highly relevant to the exchange of ideas concerning emerging cancer nursing research issues, methods, and findings. Our abstract "An Analytic Strategy for Measuring and Modeling Cancer Symptoms: A Breast Cancer Symptom Example," was given as a podium presentation and was one of the highest rated abstracts of the conference.

(E)   2005 Oncology Nursing Society (ONS) Congress. April 2005.

The ONS Congress, held in Orlando, Florida, attracted over 5,000 Oncology nurses. Attendees are not only researchers but also practicing nurses, educators, and administrators. Our abstract "Symptoms at End-of-Life among Individuals with Cancer" was given as a podium presentation.

(F)   Era of Hope 2005 DoD Breast Cancer Research Program Meeting. June 2005.

The purpose of this meeting was to provide a forum to report research studies funded by the DoD Breast Cancer Research Program. It highlighted multidisciplinary and innovative approaches to breast cancer research. I was able to interact with not only breast cancer researchers, but also clinicians and breast cancer survivors. A poster presentation of the interim results of our study, "Prevalence and Predictors of Advance Care Planning among Women with

Breast Cancer," allowed for an exchange of ideas with other attendees regarding ACP among women with breast cancer.

Abstracts based on the final results of this research are being prepared for consideration of presentation at the next Era of Hope and Oncology Nursing Society conferences.

Observations:

In summary, being mentored in preparing and presenting at conferences increased my ability to summarize and disseminate key research findings. It also developed my ability to respond extemporaneously, yet knowledgeably and succinctly, to questions regarding the research process and results. Conference attendance also enabled me to form productive relationships with other researchers conducting research in similar areas, thus increasing my ability to locate useful specific advice regarding current research issues, extending the forum for exchange of ideas regarding future research, and promoting the development of future collaborative relationships.

Research Activities

The accomplishment of Task I: Development and testing final protocol for research activities, subsections 1 ("Brochures and recruitment materials"), 2 ("Interview instruments"), 3 ("Advanced care planning intervention"), and 4 ("Obtain institutional review board approval") were detailed in the 2005 Annual Report (Task II #5).

Background

Breast cancer is the second leading cause of cancer deaths in women (American Cancer Society, 2005). Documented shortcomings in end-of-life care include deficiencies in provider/patient communication, excess reliance on aggressive treatment, and disparity between the way people experience end of life and the way they want to do so. *Advance care planning* is defined as providing directions in advance of incapacitation to guide medical decisions. An ACP document is defined as a witnessed, written document used to provide directions regarding desired health care. The two most prevalent forms of ACP documents are a durable power of attorney for health care (DPOA) or a living will (LW). Because having ACP documents reduces the initiation of undesired life support technology (Kish, Martin, Shaw, & Price, 2001), and family distress when end-of-life decisions must be made (Tilden, Tolle, Nelson, & Fields, 2001), ACP has been noted as an area in need of particular attention among individuals with cancer (Agency for Healthcare Research and Quality, 2006).

The prevalence of ACP is linked to various predictors, such as health factors, including stage and site of cancer, and comorbidity. A previous study of 872 cancer patients admitted to ICU found that completion rates of advance directives were linked to stage and site of cancer,

relapsed/progressive disease (32%, versus 16% for newly diagnosed), and hematological malignancies (30%, versus 24% for solid tumors) (Kish, Martin, & Price, 2000). Other comorbid conditions contribute to the illness experience, which may be a further predictor of ACP in cancer patients.

Additionally, it is likely that personal factors such as age, education, income, and ethnicity of the cancer patient may predict those who will or will not have ACP. Increasing age has been associated with ACP among cancer patients (Covinsky et al., 2000; Phipps et al, 2003), but findings regarding education and income are equivocal. ACP was linked with higher education and income in one study (Mezey, Leitman, Bottrell, & Ramsey, 2000), while another reported no such association (Mansell, Kazis, Glantz, & Heeren, 1999).

Ethnically differences in ACP knowledge and ACP document completion have been reported in ten studies (Kwak & Haley, 2005). One reason noted in the literature for these disparities is the substantial gap in ACP knowledge among ethnic minorities (Silveira, DiPiero, Gerrity, & Feudtner, 2000; Walters, 2000), which may be related to a lack of communication with health care providers about ACP (Cooper, Weber, Evas, & Juozapavicius, 2001). On the whole, the literature suggests that African Americans and Hispanics may benefit more than Caucasians from strategies to assist them with ACP. Initiating these discussions may result in a decrease in ethnic disparities currently evident in ACP.

It is likely that during the cancer treatment experience, symptom number, severity, and interference, as well as decreased functional status, may prompt cancer patients to implement ACP. Increasing symptoms lead to a loss of functional status, which has been associated with decreased desire for cardio-pulmonary resuscitation (Weissman et al, 1999) and with an increase in "do not resuscitate" orders (Suri, Egleston, Brody, & Rudberg, 1999).

The "Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments" (SUPPORT), the largest ACP intervention study to date, enrolled 9105 seriously ill patients with one of nine life-threatening conditions (acute respiratory failure, severe congestive health failure, severe cirrhosis, non-traumatic coma, severe chronic obstructive pulmonary disease, non-small cell lung cancer, and multiple organ system failure with sepsis or malignancy) with an average 6-month survival rate, from five different medical centers in the US. SUPPORT reported no difference between the advance directive intervention group and control group with respect to their advance directive completion rates (Teno et al., 1997).

One hypothesis for the lack of improvement in implementation of advance directives in the SUPPORT study was the stressful hospital environment of that study population. Indeed, the most promising and successful ACP intervention has been reported in less-stressful, community settings. A geographically defined, community-wide advance directive education program called *Respecting Your Choices*—which included education materials, training, and continuing

education by more than 120 local advance directive educators, access to advance directive educators at all health care organizations, common policies and practices of maintaining and using advance directive documents, and the documentation of advance directive education in the patient's medical record—yielded a change in the rate of advance directives from 15% to 85% (Hammes & Rooney, 1998). However, sustaining such a large coordinated effort outside a specifically defined geographic area has proved challenging.

This study tested the applicability of the Transactional Model of Stress and Coping (Lazarus & Folkman, 1984) in explaining ACP implementation patterns in women with breast cancer. Personal factors (such as age, ethnicity, and education), health factors (such as stage, site of cancer and comorbidity), and the cancer treatment experience (symptom number, severity, and functional status), are posited to impact ACP presence, desiring ACP information, and ACP document completion.

Specific research aims addressed regarding women participating in the RCTs

Among women with breast cancer undergoing chemotherapy, this research will:

1. describe the prevalence and predictors of ACP during and following chemotherapy and

2. determine if, compared to an attention self-management intervention, women with breast cancer exposed to a behavioral intervention that promotes self-care for symptom management are more likely to accept ACP intervention and implement ACP.

Methods

The RCTs recruited 675 individuals with solid tumor cancer diagnoses from ten different community and comprehensive cancer centers located in three states. Individuals with cancer experiencing active disease, were over the age of 21, and were undergoing chemotherapy. Individuals had to be cognitively intact, English speaking, able to complete telephone interviews, and be willing to participate the RCT screening, interviews, and intervention, as well as an audit of their medical records. Individuals under the care of a psychologist or psychiatrist with diagnosed emotional or psychological disorders were excluded.

Once individuals consented, they completed twice-weekly automated telephone calls, for up to 6 weeks, assessing symptoms until a predetermined symptom threshold was reached. If threshold was reached, individuals were contacted for a baseline interview. Upon completion of the baseline interview, they were randomized into either an experimental group or an attention self-management group. All of the interventions were 8 weeks long, with 6 contacts. The intervention was based on cognitive behavioral theory and was focused on assisting participants

to better manage their symptoms. Upon completion of the 8-week intervention, participants completed interviews at 10 and 16 weeks post baseline. This study inserted ACP questions into the baseline, 10 and 16 week interviews. Interview measures can be seen in Table 1.

Measures

Table 1. *Interview Measures*

Variable Name	Role of Variable in Analysis	Scale of Variable	Number of items
Advance Care Planning (ACP)			
Living will	PO	Di	1
Durable power of attorney	PO	Di	1
ACP communication	OC	Ca	12
Emotional Status			
Depression (CES-D)	OC	Co	20
Optimism (LOT)	OC	Co	8
Mastery	OC	Co	7
Symptoms			
Number of symptoms	OC	Co	18
Sum severity	OC	Co	18
Sum interference	OC	Co	18
Health status			
MOS SF-36	OC	Co	36
Chronic Health Conditions	OC	Co	16
Communication			
Satisfaction with provider communication	OC	Co	10
Physician Trust	OC	Co	10

Role of Variables in Analysis: PO = Primary Outcome, OC = Other Covariate
Scale of Variables: Di = Dichotomous, Ca = Categorical, Or = Ordinal, Co = Continuous

Comorbidities were assessed only at the baseline interview using a modified version of the Comorbidity Questionnaire (Katz, Chang, Sangha, Fossel, & Bates, 1996). The scale asked 14 *yes* or *no* questions (*yes* = 1; *no* = 0) about the presence of various chronic health conditions, including heart disease, hearing problems, and arthritis. It also had one open-ended question

asking if there were other major health problems. A summary score was calculated on the number of *yes* responses and other health problems reported, a higher score indicating a greater number of comorbid conditions.

Symptom interference was measured by asking participants who acknowledged experiencing a symptom: "On a scale of 0 = did not interfere to 10 = completely interfered, how much did [insert symptom] interfere in your life?" For statistical analyses, an overall symptom interference index was created by summing each participant's reports of interference across the 18 symptoms.

Emotional status was assessed using the 20-item, Likert-like Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). Scores above 16 indicate a clinical level of depressive symptomatology. The CES-D is often used in studies of individuals with cancer, providing reliable and valid data regarding the risk for depression (Hann, Winter, & Jacobsen, 1999). In this study, the reliability of the CES-D, measured by Cronbach's alpha, was .87.

Optimism was measured only at the baseline interview by the 8-item Likert scale Life Orientation Test (LOT). Four items are reverse scored and items summed to create a summary score, with higher scores indicating higher optimism. The LOT has established reliability and validity among college students and the general population (Scheier & Carver, 1985). In the current study, one item— "I'm always optimistic about my future"—was not found to be reliable and valid among the breast cancer participants; thus, it was eliminated from the summary score. The reliability of the 7-item LOT among the participants in this study was .80.

Mastery was measured using a modified 7-item Likert subscale of psychological coping resources. Three items are reverse scored and items summed, with higher scores indicating greater since of mastery (Pearlin & Schooler, 1978). The original questions were modified to assess specifically the mastery of cancer care. This modified mastery scale had an alpha of .73 among participants in this study.

General health status was evaluated using the Medical Outcomes Study (MOS) SF-36. The SF-36 measures 8 different health concepts: physical functioning, vitality, social functioning, mental health, physical role functioning, emotional role functioning, body pain, and general health (Ware, Snow, Kosinski, & Gandek, 1993). The SF-36 has been proven reliable and valid in numerous studies of cancer patients.

Satisfaction with communication with oncology providers was measured by the 10-item Likert information exchange subscale of the Princess Margaret Hospital Satisfaction questionnaire. This subscale was specifically developed to test satisfaction with providers in oncology settings (Loblaw, Bezjak, & Bunston, 1999). In the current study, the reliability of the information exchange subscale was .89.

Trust was measured using the Wake Forest Trust scale. This 10-item Likert scale has established reliability and validity in the general population with primary health care providers (Hall, Camacho, Dugan, & Balkrishnan, 2002). This was the first time the Wake Forest Trust scale has been used with individuals with cancer. Three items were found to have factor loadings lower than .40 for this study's participants. Thus, the summary score used for this study included the 7 items with acceptable factor loadings. The 7-item trust scale had a reliability of .91.

Demographics questions included age, education, race, and marital status. Data regarding cancer stage and recurrence was collected from medical records. Cancer stage was coded as *early* (stage 1 or 2) or *late* (stage 3 or 4), according to the TNM staging criteria of the American Joint Committee on Cancer (2003).

Analysis
(Statement of Work Task III #1, final analyses of data)

Aim 1 of this study was to describe the prevalence and predictors of ACP documentation, both DPOA and LW, during and following chemotherapy. Data from women with breast cancer who participated in one of the RCTs were used for this analysis. SPSS 14.0 is used for descriptive statistics. Given that ACP is expected to change over time, repeated assessment of each woman with breast cancer in the RCTs was required. In order to measure the longitudinal change of ACP during chemotherapy, a two-level, hierarchical linear model (HLM) was analyzed using HLM 6.0 (Raudenbush, Bryk, Cheog, & Congdon, 2004). HLM describes data that varies at two levels, in this case both within and between individuals (Raudenbush, & Bryk, 2002). Level 1 defines change within each woman. At level 1, the change from baseline values of rates of DPOA documents (*yes/no*) and LW documents (*yes/no*) were examined by looking at change over time in weeks divided by 10 (e.g., 10 weeks was entered as 1 and 16 weeks was entered as 1.6). As there were three time points, a linear effect of time was tested.

Individual characteristics hypothesized to impact ACP were included at level 2. A complete case analysis was used; i.e., if the participant had at least one time point, her data was included in the analysis. To render the intercept of the regression line meaningful, continuous variables such as age, CES-D, and trust were centered to the grand mean of the whole sample. Thus, an average woman is defined as one who has zero value for any continuous variable. Using data procured at both levels improved our ability to examine the effects of covariates that function in different ways at different levels of analysis (Raudenbush, 2001).

Various HLM models were tested, and the most parsimonious model with good data fit was accepted as the final model. Initial models included age, education, race, marital status, stage of cancer, recurrence of cancer, cancer metastasizes, other chronic health conditions,

optimism, depression, mastery, satisfaction with health care provider communication, and trust of health care provider.

The summary of the full model can be specified (in equation format) as:

Level-1 Model

$$Prob(Y=1|B) = P$$

$$log[P/(1-P)] = P0$$

Level-2 Model

P0 = B00 + B01*(AGE) + B02*(COLLEGE) + B03*(NONWHITE) + B04*(SINGLE) + B05*(EXPERM) + B06*(EARLY) + B07*(RECURREN) + B08*(METASTAT) + B09*(CHRONIC) + B010*(OPTIM) + B011*(CESD) + B012*(MASTER) + B013*(SATISF) + B014*(TRUST) + R0

Aim 2 is concerned with determining if women participating in the different arms of the RCTs, attention self-management intervention compared to behavioral intervention that promotes self-care for symptom management, are more likely to accept ACP intervention and implement ACP. This was examined using logistic regression to create a linear combination of the log of the odds of being in the group that is likely to accept ACP intervention or not (Tabachnick & Fidell, 2001). Prior to conducting the Logistic regression, potential baseline differences were explored using ANOVA between three groups: those who were interested in more information regarding ACP, those who were not, and those who dropped from the study before the wave 2 interview. No significant differences were seen between the groups. The dependent variable used for the Logistic regression analysis was the question asked during the wave 2 interview, "Are you interested in more information regarding advance care planning?"

Results

The mean age of the participants was 53 ± 11 years. Over half of the participants were married (n = 151, 64%), had some college education or higher (n = 178, 75%), and reported their racial background as Caucasian/white non-Hispanic (n = 199, 84%). One hundred and seventy seven women (75%) reported having at least one other chronic health condition along with their diagnosis of breast cancer. The majority of women had a diagnosis of late stage cancer (n = 177, 75%), with 28% (n = 65) of women with breast cancer having had a recurrence in their cancer. One hundred twenty five (53%) reported having metastatic breast cancer. Demographic descriptives can be seen in Table 2.

Table 2: *Demographic Information (N = 236)*

	Min -Max	Mean (SD)
Age	28 - 90	57 (11.8)
Number of chronic health conditions	0 - 7	1.67 (1.46)

	N	Percent
Educational level		
Grade school	1	.5%
Some high school	11	4.5%
High school	46	19.5%
Some college or technical training	72	30.5%
College	53	22.5%
Graduate degree	53	22.5%
Marital status		
Never married	32	14%
Married	151	64%
Divorced or separated	38	16%
Widowed	13	6%
Living together	2	1%
Race		
Caucasian or White	199	84%
African American or Black	26	11%
Hispanic or Latino	3	1%
Native American	4	2%
Missing data	4	2%

The majority of women with breast cancer participating in the RCTs had heard about ACP (n = 208, 88%). The number of ACP knowledge sources ranged from 0 to 7 with a mean of 1.3 and a SD of 1.4. The most common source of ACP knowledge was the hospital (n = 79, 34%), followed by a family member (n = 63, 27%), and then a lawyer (n = 49, 21%). Seventy-six

women (32%) reported having a DPOA, and 71 (30%) reported having a LW. One hundred forty-one participants (60%) reported talking to someone about their advance care plans. Most commonly, these women had shared their advance care plans with a family member (n = 136, 58%) or a friend (n = 35, 15%). Few, however, had shared their ACP with the hospital (n = 6, 3%), a doctor (n = 10, 4%), or a nurse (n = 5, 2%).

Variables associated with ACP documents over time

For the LW final model, age ($\hat{\beta}_{01}$ = .085, p <.000), optimism ($\hat{\beta}_{02}$ = .17, p = .007), mastery ($\hat{\beta}_{03}$ = -.15, p = .011), and trust ($\hat{\beta}_{04}$ = .12, p = .028) were found to be significant predictors. Older women were more likely to have a LW (Figure 1). Women with breast cancer with a more optimistic view of life were more likely to have a LW, as were those who had a higher level of trust in their health care provider (Figure 2). Interestingly, women who reported lower feelings of mastery over their cancer care were more likely to have a LW; however, none of the health variables such as stage of cancer, recurrence of cancer, nor whether the cancer was metastatic were found to be significant predictors of having a LW. There was no significant change over time in rates of LW documentation.

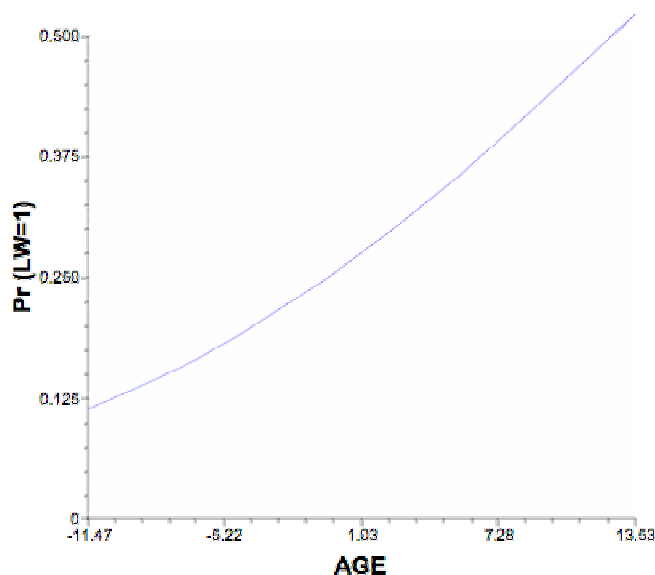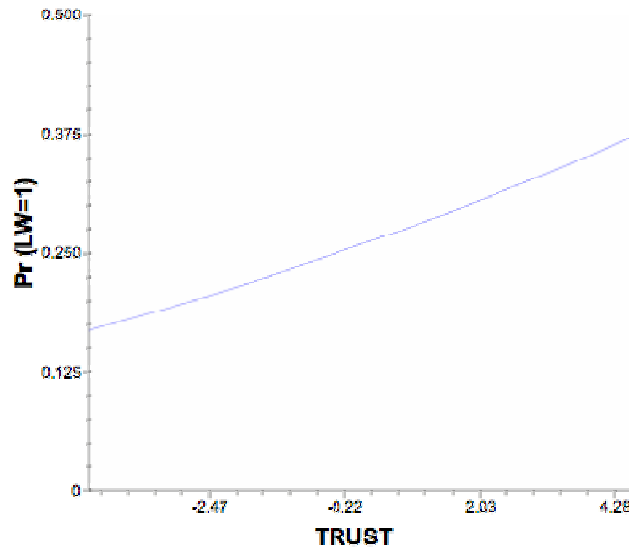*Figure 1.* Association of age and probability of having a LW

Figure 2. Association of oncology provider trust and probability of having a LW

For the DPOA final model, significant predictors of having a DPOA included age ($\hat{\beta}_{01}$ = .075, p <.000), being an ethnic minority ($\hat{\beta}_{02}$ = -1.22, p =.064), optimism ($\hat{\beta}_{03}$ = .195, p =.002), and mastery ($\hat{\beta}_{04}$ = -.086, p =.089). There was no significant change in DPOA documentation during the 16 weeks of the study. Older and more optimistic women were more likely to have a DPOA. Ethnic minorities were less likely to have a DPOA, had lower ratings of mastery over their cancer care, and less optimism (Figure 3 and 4).

Figure 3. Association of mastery with cancer care and probably of having a DPOA by race
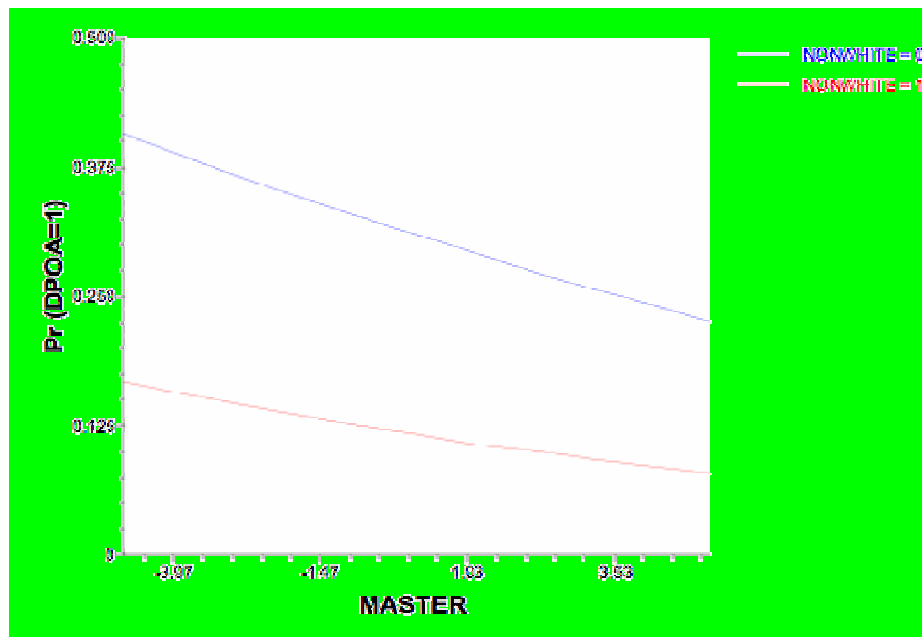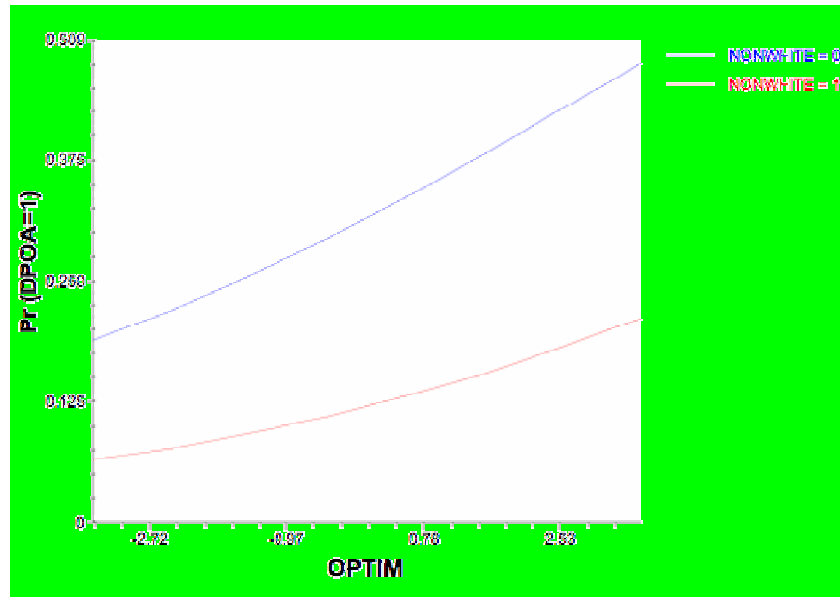
Figure 4. Association of optimism and probability of having a DPOA by race
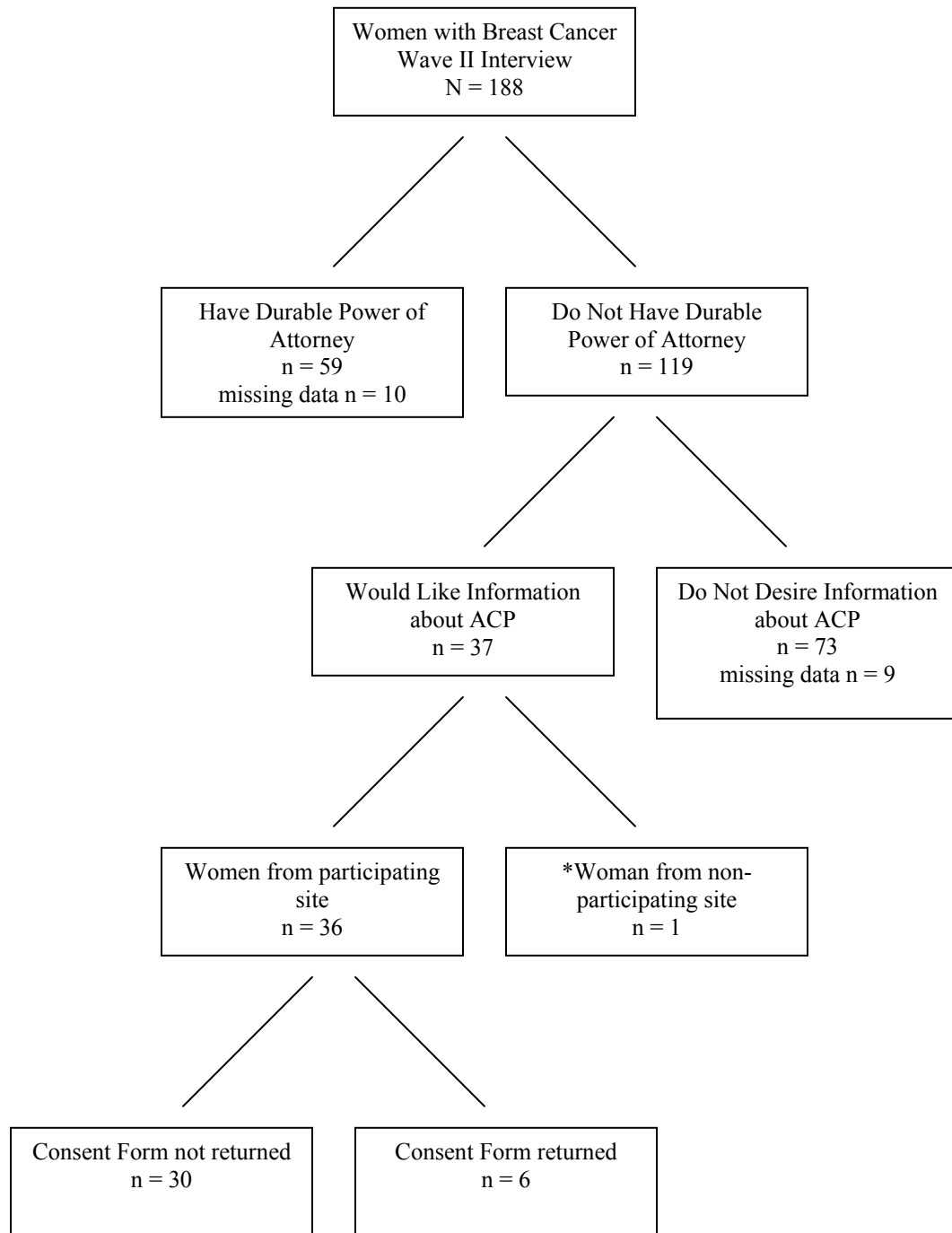

Variables associated with acceptance of ACP intervention

A logistic regression was used to examine variables associated with the probability of the acceptance of ACP intervention. All independent variables were entered into the logistic regression equation simultaneously. Data from 128 women with breast cancer who completed the wave 2 interviews were available for analysis: 31 agreed to more information about ACP, 97 did not desire information, and 60 were missing data. A test of the full model with all independent variables against the unconditional model was statistically reliable—chi square (15, N = 126) = 26.81, p = .03—indicating that the predictors, as a set, reliably distinguished between women who desired ACP information and those who did not. However, prediction success for those who desired ACP information was unimpressive, with only 19% prediction success. The model was 92% successful in predicting those who did not desire ACP information. According to the Wald criterion, only depression ($z = 4.1$, p = .04) and satisfaction with health provider communication ($z = 5.2$, p = .02) were significantly associated with desiring ACP information. Women with breast cancer undergoing chemotherapy who were more depressed had a greater probability of desiring information about ACP. Additionally, women who had lower satisfaction with their oncologist's communication also had a greater probability of desiring information about ACP.

Recruit women with breast cancer from ongoing RCTs
(Statement of Work Task II #1)

As originally proposed, at the week 10 interview of either *Family Home Care for Cancer –
A Community-Based Model* (R01 CA-79280) or *Automated Telephone Monitoring for Symptom
Management* (R01 CA-30724), women with breast cancer who did not currently have ACP
documentation were asked if they would like more information about ACP (n = 119). Thirty-
seven women indicated in the affirmative, and were sent information about the ACP Project. Six
women returned consent forms and completed the intervention. See Figure 5 for flow of women
with breast cancer recruited from the two RCTs.

Figure 5. Flow chart of women with breast cancer recruited from the RCTs

```
                    ┌─────────────────────────┐
                    │  Women with Breast Cancer │
                    │     Wave II Interview     │
                    │         N = 188           │
                    └─────────────────────────┘
                       /                  \
        ┌──────────────────────┐   ┌──────────────────────┐
        │  Have Durable Power of │   │  Do Not Have Durable  │
        │        Attorney        │   │   Power of Attorney   │
        │        n = 59          │   │        n = 119        │
        │  missing data n = 10   │   └──────────────────────┘
        └──────────────────────┘        /              \
              ┌──────────────────────┐   ┌──────────────────────┐
              │ Would Like Information │   │ Do Not Desire Information │
              │     about ACP          │   │       about ACP        │
              │      n = 37            │   │        n = 73          │
              └──────────────────────┘   │   missing data n = 9   │
                   /          \          └──────────────────────┘
      ┌──────────────────────┐   ┌──────────────────────┐
      │ Women from participating │   │ *Woman from non-       │
      │        site            │   │  participating site    │
      │       n = 36           │   │        n = 1           │
      └──────────────────────┘   └──────────────────────┘
           /            \
  ┌──────────────────┐   ┌──────────────────┐
  │ Consent Form not  │   │ Consent Form      │
  │    returned       │   │   returned        │
  │    n = 30         │   │    n = 6          │
  └──────────────────┘   └──────────────────┘
```

*Note: The RCTs recruited individuals from ten sites. Two of the ten did not participate in having women with breast cancer approached with information about the ACP pilot intervention. One woman who indicated that she would like information about ACP was at a site not participating in the ACP pilot intervention. Thus, she was sent ACP information but not information regarding the study.

One woman recruited from the RCTs dropped after the ACP intervention, due to being too ill to complete the follow up interview. Thus, five women with breast cancer recruited from the RCTs completed the ACP project.

Modification of recruitment and retention strategies
(Statement of Work Task II #6)

To be recruited from the ongoing RCTs for the ACP pilot intervention, a woman with breast cancer must not have ACP documentation, and must answer in the affirmative to desiring information about ACP. This recruitment from the ongoing RCTs is only in relation to answering Research Aim 3 of the ACP study: to test the effectiveness of ACP information intervention in increasing ACP implementation, in the presence of varying levels of stressors and exposure to behavioral intervention or attention self-management intervention.

Issues that may have contributed to the low numbers of women with breast cancer recruited from the RCTs are as follows:

1. Question asked during week 10 interview.
   The question at the week 10 interview asked, "Do you want more information about ACP?" Current legislation requires that upon admission to a hospital people are asked if they have ACP documentation and, if not, are provided information about ACP. As the majority of the women with breast cancer had surgery as part of their treatment, which requires a hospital admission, it is probable that they had been provided ACP information in the past. Thus, potentially, other questions such as, "Would you like assistance with completing advance care planning documents?" may have elicited greater interest in the ACP pilot intervention.

2. Lack of follow up after study information and consent forms were sent.
   Follow up phone calls and a letter to be sent as follow up to women with breast cancer who did not return the consent forms were originally proposed. However, sharing the personal information of phone number and name of potential participants from the RCTs before they signed a consent form would have been a violation of privacy as defined by HIPPA. Thus, no follow up could occur after ACP study information was initially sent.

As the number of women with breast cancer recruited from *Family Home Care for Cancer—A Community-Based Model* (R01 CA-79280) or *Automated Telephone Monitoring for Symptom Management* (R01 CA-30724) fell significantly short of the five to six per month proposed, modification of recruitment strategies were put into place.

Recruitment from outside the ongoing trials modified the population base on which Aim 3—"test the effectiveness of an advance care planning intervention"—was tested. The population was modified to recruit women with breast cancer from support groups or other mailing lists of women with breast cancer. This modification allowed for greater generalizability of Aim 3 study findings to women with breast cancer; however, it lost the richness of the additional data derived from the ongoing RCTs.

Additionally, since women recruited from support groups had not completed the ongoing RCTs interviews, which provided baseline data for the ACP pilot intervention for women recruited from the RCTs, women recruited from support groups underwent a baseline interview. Because of these differences in procedures, separate consent forms were used for women recruited from support groups and women recruited from the RCTs. Hence, a revision to the protocol was written which included revisions to recruitment, informed consent procedure, and procedures, with the addition of a baseline interview for women recruited from support groups. The modification to procedure was approved by DoD HSRRB on March 1, 2005.

Support group recruitment

Eighteen breast cancer support groups were contacted regarding their interest in having information shared about the ACP study with support group participants. Four support groups indicated that they did not want to provide study information to their support group members. Three reasons were given for refusal: (1) they felt ACP information not to be of interest to support group members, (2) they already had an ACP educational program in place at their institution, or (3) they felt the content would potentially distress their participants. Table 1 lists the names of the participating support groups, the number of women recruited from each support group, and the attrition during the process of the ACP pilot intervention.

A convenience sample was recruited from the fourteen participating support groups. Inclusion criteria of women with breast cancer from support groups were that the women must be age 21 or older; with English as their dominant language; able to speak, read, and comprehend English; be cognitively intact as evidenced by responses; have a working telephone; have at least a P.O. Box where study information could be sent; and be able to give informed consent.

Women associated with support groups were recruited by written and oral information provided at support group meetings, written announcements in newsletters, and letters of invitation sent by leaders of the support group to members. Brochures describing the ACP study and consent forms were also available for support group members to pass out to their networks of women with breast cancer.

Those women with breast cancer who indicated interest in receiving information about ACP and who contacted the PI were sent a packet containing a cover letter, a brochure

(describing the study), and two consent forms (one to sign and return in an enclosed, pre-addressed, stamped envelope, and the other for reference).

Opportunities to discuss the study were provided by: (1) the PI's presence at support group meetings and (2) the inclusion in the information packet of the PI email address and a toll-free number for contacting the PI to ask questions or discuss the study before making a decision to participate.

If the signed consent form was not returned in two weeks, telephone contact was attempted by the PI over two weeks, calling on various days and at various times during the day. No more than three messages were left. If the potential participant was reached by telephone, she was asked about interest in the study and mailing back the consent form.

Procedures
(Statement of Work Task II #2, Task II #3, and Task II #4)

Interviews

Upon receipt of a signed consent form, a baseline interview was scheduled. The interview was administered over the telephone by the PI using a computer-assisted telephone interview program. The interview took approximately 45-60 minutes to administer and was broken up into sections for participants who became fatigued during the interview. Interview measures used were the same as in the RCTs, as described above.

Intervention

Each participant was mailed five copies of the *Five Wishes* ACP literature: one copy to keep and the others to give to health care providers, their designated health care advocate, or family members. The *Five Wishes* was chosen because it assists people in completing ACP. The *Five Wishes* is a well-constructed, user-friendly, multi-dimensional legal document recognized in 37 states. Additionally, the *Next Steps* guide was included in the mailing, as it provided information and guidance about how to communicate with family members, friends, and health care providers about ACP. A cover letter requested that the participant keep the materials by the telephone for the intervention telephone interview.

Within one week after the ACP literature should have been received, a PhD-prepared nurse with experience in ACP telephoned to conduct an approximately hour-long telephone ACP educational intervention, using a standardized script, reviewing the *Five Wishes* and *Next Steps* literature. Completion of the *Five Wishes* constitutes completion of a LW and DPOA. Within the *Five* Wishes brochure, *Wish One* is a Durable Power of Attorney for Health Care, in which the patient designates another person, a healthcare proxy, to make medical decisions when the patient is no longer able to do so. Information covered includes sections on picking the right

person to be a health care agent, the decisions the patient wants made for her when she is no longer able to speak for herself, and what to do when a change of health care proxy is desired.

Wish Two is a Living Will, which formally documents the kind of medical treatment a patient wants if she becomes seriously ill and can no longer communicate. A definition of life-support treatment is included. Wish Two also covers four scenarios to assist the patient to identify types of medical treatment desired by circumstance: close to death, permanent and severe brain damage and not expected to recover, in a coma and not expected to wake up or recover, and in another condition under which the patient would not desire life-support treatment. This last condition deals specifically with the quality of life that the patient desires, such as when she is no longer able to take care of herself mentally or physically, or the costs and burdens of life-support treatments are too much and no longer worth the benefits.

Wishes Three and *Four* describe potential personal and spiritual wishes. Wish Three information covers desires for how comfortable the patient would like to be, including the amount of pain control she desires. Wish Four covers spiritual and personal wishes, such as the desire for prayer and visitation by religious leaders. Additionally, it covers the desired place of death.

Wish Five is an opportunity to record how the patient wishes to be remembered. Wish Five offers the opportunity to document forgiveness and love to family and friends, how the patient would like to be remembered, and desires for funeral or memorial services.

The *Next Steps* guide was used to provide each woman with assistance in communicating with her family and health care providers about her *Five Wishes*, and in filing it in her medical record. This guide includes topics such as, "How to talk with loved ones about *Five Wishes*," "How to talk with doctors about *Five Wishes*," and "Answers to questions about *Five Wishes*."

One month following ACP intervention, a follow-up interview was performed to assessed whether or not the *Five Wishes* information had been shared with health care providers and family members and to collect data on other possible co-variates (see Table 2, "After ACP intervention" column).

Quality Assurance

Quality assurance of taped interviews and interventions were completed each month and provided to my mentor for evaluation. My mentor selectively listened to tapes and provided oral and written feedback to assist with improvement of delivery of interventions and data collection during interviews. Files were also audited each month for deviations from protocol.

Support Group Analysis

Aim 3 is concerned with testing the effectiveness of the ACP intervention among women recruited from breast cancer support groups. Logistic regression was used to evaluate the probability of the presence of a DPOA or LW after the intervention, based on the combination of values of the predictor variables.

Support Group Results

Eighty-nine women from support groups agreed to participate and signed consent forms. Eighty-three were recruited during support group meetings, and an additional six were recruited by mailed support group newsletter announcements. Nine women dropped either before or during the baseline interview. Six women were unable to be reached for the baseline interview, and were thus dropped. One woman withdrew due to being too busy to participate; one withdrew due to being recently diagnosed with lung cancer and feeling overwhelmed; and one withdrew due to unhappiness with the interview questions. Two women were dropped due to an inability to schedule the intervention conveniently, and an additional three women did not complete the follow up interview. Thus, 75 women (84%) completed the study.

The mean age of the ACP pilot intervention participants was 56 ± 11 years. Approximately one third of participants were divorced or separated (n = 28, 35%) another 28 were married (35%), nine (11%) were widowed, nine (11%) were in same sex partnerships, and the remaining 7 (9%) were single. Over half had some college education or higher (n = 46, 57%). Eighty percent of participants (n = 60) had an income of 50,000 or lower. The racial background of participants were 51% (n = 41) African American, 48% (n = 38) Caucasian, and one (1%) Native American. Slightly fewer than half of the women had a diagnosis of late stage cancer (n = 34, 45%), with 34% (n = 27) of women reporting having had a recurrence in their cancer. Demographic descriptives by race can be seen in Table 3.

Table 3. *Demographics of ACP Pilot Intervention for Support Group Participants by Race*

	African American (n = 41)		Caucasian (n = 38)	
	Min -Max	Mean (SD)	Min -Max	Mean (SD)
Age	19 - 78	57 (12.6)	34 - 73	56 (9.4)
Number of chronic health conditions	0 - 8	3 (2.1)	0 - 7	2.7 (1.9)
	N	Percent	N	Percent
Educational level				
Some high school	9	22%	3	8%
High school	16	39%	5	13%
Some college or technical training	11	27%	11	29%
College	2	5%	5	13%
Graduate degree	3	7%	14	37%
Marital status				
Never married	7	17%		
Married	16	39%	11	29%
Divorced or separated	12	29%	15	40%
Widowed	6	15%	3	8%
Lesbian			9	24%
Income				
Less than 24,999	25	61%	12	32%
25,000 – 49,999	9	22%	13	34%
50,000 – 74,999	3	7%	6	16%
75,000 – 99,999			4	11%
Over 100,000			2	5%
Stage of cancer				
Early	15	32%	25	45%
Late	23	56%	11	50%
Missing data	3	7%	2	5%
Reoccurrence				
Yes	12	29%	15	39%
No	29	71%	23	61%

At baseline, 49 (61%) of the women recruited from support groups indicated that they had heard about ACP. The most common source of ACP knowledge was the hospital (n = 26, 33%), followed by a family member (n = 12, 15%). After the intervention, all participants reported having ACP knowledge. At the FU interview, one month after ACP intervention, 46 women (58%) had completed a DPOA and a LW. Women were most likely to discuss ACP with their family (n = 47, 59%) or friends (n = 13, 16%); however, they were not likely to discuss their ACP with the hospital staff (n = 7, 9%) or other health care professionals (n = 8, 10%). Reasons women gave for not completing either a DPOA or LW can be seen in Table 4. The most common reason was that the woman was not interested in completing ACP documents at this time in her life.

Table 4. *Barriers to Completing ACP Documentation*

Reason for not completing ACP documentation	n =
Not interested in completing ACP at this time	12
Did not find the right time/too busy	4
Not feeling well/too tired from chemotherapy	3
Not able to get family together	3
Not able to find witnesses	2
Family member (husband/daughter) sick	2
Did not get around to it	1
Did not think about it again	1
Could not decide on a health care advocate	1
Family not supportive of ACP	1
Total	30

Variables associated with completing ACP documentation

A logistic regression was used to examine the variables associated with completing both a DPOA and a LW. All independent variables were entered into the logistic regression equation simultaneously. Data from 75 women with breast cancer who completed the ACP pilot intervention study were available for analysis: the 46 completed ACP documentation and the 29 who did not; the 5 who dropped during the study were considered as missing data. A test of the full model with all independent variables against the unconditional model was statistically reliable—chi square (11, N = 75) = 29.55, p = .002—indicating that the independent variables, as

a set, reliably distinguished between women who completed ACP and those who did not. The variance in completing ACP documentation accounted for was 37%. Prediction success for those who completed ACP documentation was 87%. The model was less successful in predicting those who did not complete ACP documentation (63%). According to the Wald criterion, the number of chronic health conditions ($z = 4.3$, p = .04), the stage of breast cancer ($z = 5.46$, p = .02), the date of diagnosis ($z = 8.02$, p = .005), and reoccurrence of breast cancer ($z = 6.37$, p = .01) were significantly associated with completing ACP documentation. In summary, for women with a diagnosis of breast cancer recruited from support groups, decreased health, such as advanced stage of breast cancer and increasing number of other chronic health conditions were associated with a higher probability of completing ACP documents.

Preparation of manuscripts
(Statement of Work Task III #2)

Preparations of manuscripts based on this final report are underway. Three manuscripts are planned based on the findings reported above. Additionally, when the chart audit data from *Family Home Care for Cancer—A Community-Based Model* (R01 CA-79280) and *Automated Telephone Monitoring for Symptom Management* (R01 CA-30724) becomes available in December, an additional manuscript is planned. This manuscript will examine the variables associated with having ACP documents in the medical record as well as the congruence between having ACP documents and their presence in the medical record.

Key Research Accomplishments

- Innovative statistical methods were tested to better examine the symptom trajectory among women with breast cancer over time by embedding an Item Response Model into a Hierarchical Linear Model
- Found that trust in oncology providers was significantly associated with having ACP documents among women with breast cancer undergoing chemotherapy
- Successful recruitment of over 50% African American women with breast cancer into the ACP pilot intervention project
- Determined the effectiveness of the ACP intervention in improving ACP knowledge and ACP document completion rates

List of Personnel Receiving Pay from Research Effort

Ardith Doorenbos, PhD, RN

Reportable Outcomes

Position

Assistant Professor, University of Washington School of Nursing, commencing September, 2006

Awards and honors

Top ranked abstract: 2004 Oncology Nursing Society Congress

Exceptional New Investigator Award: Midwest Nursing Research Society: End-of-Life/Palliative Care Research Section 2006

Fellowship

National Institute of Health Fellowship 2004
Summer Institute on Randomized Clinical Trials Involving Behavioral Interventions

Publications

Doorenbos, A. Z., Verbitsky, N., Given, B., & Given, C. W. (2005). An analytic strategy for modeling multiple item responses: A breast cancer symptom example. *Nursing Research, 54,* 229-234.

Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. (2006). Physical functioning: Effect of behavioral intervention for symptoms among individuals with cancer. *Nursing Research, 55,* 161-171.

Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. (in press). Symptoms in the last year of life among individuals with cancer. *Journal of Pain and Symptom Management*.

Presentations

Poster presentations

Doorenbos, A. Z., Given, B., Given, C. W., Wyatt, G., Gift, A., Rahbar, M., et al. (September, 2004). *Impact of end-of-life care for caregivers of family members with cancer.* Michigan Cancer Consortium, Lansing, MI.

Doorenbos, A. Z., Given, C., & Given, B. (June, 2005). *Prevalence and predictors of advance care planning among women with breast cancer*. Era of Hope 2005, DoD Breast Cancer Research Program Meeting, Philadelphia, PA.

Doorenbos, A.Z., Given, C. W., & Given, B. (November, 2005). *Prevalence and predictors of advance care planning among women with breast cancer*. Michigan Cancer Consortium, Lansing, MI.

Keehne-Miron, J., Given, C. W., Given, B. A., vonEye, A., & Doorenbos, A. Z. (October, 2005). *The prediction of symptom severity for breast and lung cancer chemotherapy patients*. 38th Annual Great Lakes Cancer Nursing Conference of the American Cancer Society, Novi, MI.

Doorenbos, A. Z., Given, C. W., & Given, B. (November, 2005). *Symptoms at end of life among individuals with cancer.* The 58th Annual Scientific Meeting of The Gerontological Society of America, Orlando, FL.

Paper presentations

Doorenbos, A. Z., Given, B., Given, C. W., Jeon, S., & Rahbar, M. (October, 2004). The impact of a cognitive behavioral intervention on symptom-based limitations and physical function: Results of a randomized clinical trial. 2004 National State-of-the-Science Conference, Washington, DC.

Doorenbos, A. Z., Given, B., Given, C. W., Wyatt, G., Gift, A., Rahbar, M., et al. (November, 2004). *Impact of end-of-life care for caregivers of family members over 65 with cancer.* Gerontological Society of America 57th Annual Scientific Meeting, Washington, DC.

Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. (February, 2005). *An analytic strategy for measuring and modeling cancer symptoms.* 8th National Conference on Cancer Nursing Research, Fort Lauderdale, FL.

Doorenbos, A. Z., Given, B., Given, C., & Verbitsky, N. (April, 2005). *Symptoms at end of life among individuals with cancer*. Oncology Nursing Society 2005 Congress, Orlando, FL.

Doorenbos, A. Z., Given, C. W., Given, B., & Sherwood, P. (November, 2005). *Aging issues in cognitive behavioral interventions for symptoms with cancer patients*. The 58th Annual Scientific Meeting of The Gerontological Society of America, Orlando, FL.

Conclusions

Among women with breast cancer undergoing chemotherapy, age was a significant predictor of the presence of both ACP documents: a DPOA and a LW. This result supports what has been previously reported in the literature (Covinsky et al, 2000; Phipps et al, 2003). The mastery scale used in this study was modified so that it assessed specifically the mastery women felt they had over their breast cancer experience. As women reported feeling less mastery over their breast cancer experience, the probability of having ACP documentation increased. However, contrary to what has been previously reported, in this study, health factors such as stage of breast cancer, recurrence of cancer and other co-morbidities were not found to be predictors of ACP documentation. Thus, for women participating in the RCTs for symptom management, the overall mastery of the total cancer experience was a more important predictor of ACP documentation than were specific health factors.

Among women with breast cancer, trust of their oncology providers was a significant predictor of having ACP documentation. As trust increased, so did the probably of having both a LW and a DPOA. Ethnicity was only a predictor of a DPOA, not of a LW. When looking at trust and ethnicity together as predictors of DPOA completion, ethnic minorities reported less trust of the oncology providers. Thus, improving oncology provider trust is a potentially promising mediator of ACP document completion among women with breast cancer undergoing chemotherapy. This research further suggests that improving the trusting relationship between oncology providers and women with breast cancer is especially important among ethnic minorities.

Predictors of women with breast cancer undergoing chemotherapy who desired information regarding ACP were those who scored higher on the CES-D and had low satisfaction with the communication with their oncology provider. This may indicate that they were unhappy with their cancer treatment experience in general and considered ACP a way to ensure that their wishes regarding treatment would be honored. Overall, women who desired information about ACP during their chemotherapy treatment were few (24%, n = 31). Undergoing breast cancer treatment is stressful, and perhaps a difficult time to think about completing ACP documents, a consideration which may have contributed to the low rate of recruitment of women with breast cancer into the ACP pilot intervention project from the RCT studies. As the Transactional Model of Stress and Coping posits, if stress is overwhelming and coping resources are few, then a woman with breast cancer would be less likely capable of completing ACP documentation. This hypothesis is bolstered by the findings of the SUPPORT study, which suggest that the stressful hospital environment may have been a reason for the lack of implementation of ACP (Teno et al, 1997).

Recruitment of women having a diagnosis of breast cancer to the ACP pilot intervention project was more successful from support groups. Recruitment was particularly successful among African-American and Lesbian women with breast cancer. Thirty-seven percent of African-American women, compared to 87% of Caucasian women, with breast cancer reported having knowledge of ACP documents at the baseline interview. This supports findings of ethnic differences in ACP knowledge reported in previous studies (Kwak & Haley, 2005). In general, African-American women were interested in knowing more about ACP. This supports the conclusions from a previous study that explored patient preferences for communication with health care providers about end-of-life decisions, the findings of which suggested that African Americans were more likely than Caucasians to desire discussions about advance directives (Hofmann et al, 1997).

The ACP pilot intervention was successful among all women in improving ACP knowledge. Fifty-eight percent (n = 46) of women completed ACP documentation after receiving the ACP intervention. A greater percentage of Caucasian women (n = 27, 71%) completed ACP documents after intervention than did African-American women (n = 18, 44%). There was a greater motivation for Lesbian women, who in this study were all Caucasian, to complete ACP documents. This motivation came from the desire to protect their partner's rights to make heath care decisions. Lesbian women with breast cancer reported experiences of other Lesbians, who had not completed ACP, in which the family had come in and taken over the end-of-life decisions and excluded the life-long partner.

Predictors of ACP document completion among the women with breast cancer recruited from support groups were the health factors of number of chronic health conditions, stage of breast cancer, reoccurrence of breast cancer, and closeness to the date of breast cancer diagnosis. This suggests that outside the stressful experience of breast cancer treatment among women participating in support groups, health factors are important in increasing the probability of completing ACP documents.

In summary, this Clinical Research Nurse Award provided support needed for breast cancer training to accelerate my development as an evolving breast cancer nurse scientist. The ACP research was innovative, as it integrated questions regarding ACP into two RCTs: *Family Home Care for Cancer: A Community-Based Model for Symptom Management*, Dr. C. Given, Co-PI (R01 CA079280); and *Automated Telephone Information and Monitoring of Symptoms,* Dr. C. Given, PI (R01 CA030724). ACP questions were inserted into these two trials of behavioral interventions for symptom management at the baseline, week 10, and 16 interviews. This allowed us to prospectively examine ACP documentation as women with breast cancer proceeded through chemotherapy. Thus, the results of the research offered unique insights into what personal and health factors increase the probability of ACP document presence and interest

in ACP information among women with breast cancer undergoing chemotherapy. Future intervention research among women with breast cancer undergoing chemotherapy is needed, to explore ways to increase trust in oncology providers, especially among African-American women.

Additionally, this research examined how ACP might be integrated into breast cancer support groups. Among the innovative aspects of this research is its focus on ACP intervention in a community sample of non-hospitalized women with breast cancer. These women have received a possibly life-limiting diagnosis of cancer, potentially serving as a cue to action for ACP implementation. Support group findings supported the effectiveness of the ACP intervention in increasing knowledge and ACP document completion. Continued ACP intervention research is warranted, especially among African-American women with breast cancer, to improve both knowledge and ACP document completion rates. This will further reduce end-of-life disparities and promote women's ability to have control over the care they desire at end of life.

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Appendices

1. Doorenbos, A. Z., Verbitsky, N., Given, B., & Given, C. W. (2005). An analytic strategy for modeling multiple item responses: A breast cancer symptom example. *Nursing Research, 54,* 229-234.

2. Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. (2006). Physical functioning: Effect of behavioral intervention for symptoms among individuals with cancer. *Nursing Research, 55,* 161-171.

3. Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. (in press). Symptoms in the last year of life among individuals with cancer. *Journal of Pain and Symptom Management*.

An Analytic Strategy for Modeling Multiple-Item Responses

A Breast Cancer Symptom Example

Ardith Z. Doorenbos ▾ Natalya Verbitsky ▾ Barbara Given ▾ Charles W. Given

► **Background:** Item Response Theory (IRT) is increasingly applied in health research to combine information from multiple-item responses. IRT posits that a person's susceptibility to a symptom is driven by the interaction of the characteristics of the symptom and person. This article describes the statistical background of incorporating IRT into a multilevel framework and extends this approach to longitudinal health outcomes, where the self-report method is used to construct a multi-item scale.

► **Methods:** A secondary analysis of data from 2 descriptive longitudinal studies is performed. The data include 21 symptoms reported across time by 350 women with breast cancer. A 3-level hierarchical linear model (HLM) was used for the analysis. Level 1 models the item responses, consisting of symptom presence or absence. Level 2 models the trajectory of each individual, representing change over time of the IRT-created latent variable symptom experience. Level 3 explains that trajectory using person-specific characteristics such as age and location of care. The purpose of the analysis is to examine if older and younger women with breast cancer differ in their symptom experience trajectory after controlling for location of care.

► **Results:** Fatigue and pain were the most prevalent symptoms. The symptom experience of women with breast cancer was found to improve over time. Neither age nor location of care was significantly associated with the symptom experience trajectory.

► **Discussion:** Embedding IRT into an HLM framework produces several benefits. The example provided demonstrates benefits through the creation of a latent symptom experience variable that can be used either as an outcome or as a covariate in another model, examining the latent symptom experience trajectory and its relationship with covariates at the individual level, and managing symptom nonresponse.

► **Key Words:** cancer symptoms · hierarchical linear model · Item Response Theory · women with breast cancer

I n studying symptoms of disease, exposure to risk, behavior, beliefs, and attitudes, nursing researchers frequently have to combine a number of item responses. In such studies, participants may be repeatedly assessed over time; nested within social settings, such as hospitals, nursing homes, or communities; or both. With social settings in particular, a wide variability of gathered data results from a sometimes unknown multitude of sources. Missing item-level data are often unavoidable as well. Some examples of questions that arise in such cases, requiring robust analytical methodologies are: How does the symptom experience of women with breast cancer change over the course of the chemotherapy treatment? Does age affect engagement in risky behaviors that contribute to AIDS/HIV? Do individual beliefs and cultural attitudes influence the acceptance of differing end-of-life care paradigms?

Item Response Theory

Item Response Theory (IRT) was developed in the 1980s in educational research to address some of the issues of measurement practices in scoring tests (McDonald, 1999; van der Linden & Hambleton, 1997). The IRT models postulate that characteristics of a test item, such as its difficulty, interact with an individual's ability or trait to determine the probability of a correct response to that item (Cheong & Raudenbush, 2000; Lord, 1980). The simplest IRT model, the Rasch model, has only one parameter per item, namely difficulty. The Rasch model makes the assumption that each item is equally discriminating. When this assumption is true, the resulting scale has a clear interpretation—that difficult items will be answered correctly less frequently than easy items. Besides an item-difficulty scale, the IRT can also provide estimates of latent abilities

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that can be studied as either explanatory or outcome variables in other models. Of particular significance to this class of analysis, IRT reduces the skewness that commonly arises in composite measures, such as the sum or proportion. This framework has recently been applied to health outcomes (Fortinsky, Garcia, Sheehan, Madigan, & Tullai-McGuiness, 2003; Hays, Morales, & Reise, 2000).

> *Item Response Theory (IRT) was developed in the 1980s to address measurement practices in scoring tests.*

Hierarchal Linear Models

Statistical models that account for nesting of data (e.g., hierarchical linear models [HLMs]) have been growing in popularity (Raudenbush & Bryk, 2002). There has been an increase in the use of HLM in nursing research, especially in research examining patient and organizational outcomes (Cho, 2003; Cho, Ketefian, Barkauskas, & Smith, 2003; Whitman, Davidson, Sereika, & Rudy, 2001). In the past, when confronted with data on individuals nested in organizations, a researcher had to decide whether to perform the analysis at the individual level, thus ignoring the nested structure of the data, or whether to aggregate the variables to the higher level, thus ignoring individual variation within the organizations. In using an HLM analysis, the researcher no longer has to decide at which level to perform the analysis. This avoids problems of misestimating standard errors and of incorrect statistical inference.

There are several benefits of incorporating the IRT into an HLM framework for nursing researchers: (*a*) It includes the ability to examine multiple dimensions of abilities, traits, or symptoms; (*b*) it can separate the variation between social settings, such as hospitals, nursing homes, or communities, from the variation between individuals who are nested within these settings; (*c*) it provides a way to examine the measurement error in the assessment of social settings where individuals are used as informants about their social setting; (*d*) it allows the researcher to examine the relationship between explanatory variables at various levels (e.g., individual or setting) and the ability or trait; (*e*) it provides a framework for incorporating repeated observations of item responses to examine changes in the latent ability over time; and (*f*) the combined framework also provides a way to manage item nonresponse (Raudenbush & Bryk, 2002). These items exemplify the benefits of embedding an IRT model into an HLM framework as a tool for studying symptoms and other self-reported health behavior. A more detailed theoretical discussion regarding incorporating the IRT into an HLM framework can be found in Raudenbush, Johnson, and Sampson (2003), and Johnson and Raudenbush (in press).

Having described the statistical background of incorporating IRT into an HLM framework, the purpose of this article is to illustrate this methodology using an example of the symptom experience for women with breast cancer. This demonstrates the methodology by extending the approach to longitudinal data with health outcomes, where the self-report method is used to construct a multi-item scale. The aim of the analysis is to examine if older and younger women differ in their symptom experience trajectory after controlling for location of care.

An Example: Three-Level HLM Model Incorporating a Symptom IRT

An important aspect of symptom research is how symptom experience varies over time according to the characteristics of the individual and setting. For example, the symptom experience may change differently over time for each woman with breast cancer. Age may influence the relationship, as older women may tend to report fewer symptoms and thus have better symptom experience than younger women at diagnosis and start of chemotherapy. However, younger women may tend to return to the prediagnosis symptom experience faster than older women. Additionally, medical care can affect the symptom experience trajectory. Women receiving care at urban hospitals may have a greater accessibility to medical treatments and thus experience fewer symptoms overall than those at rural hospitals. Incorporating IRT into an HLM framework allows us to examine these and other similar questions.

This example describes a longitudinal Rasch model, which incorporates repeated measures on 21 symptoms at four time points over a 1-year period. Following HLM terminology, we have symptoms at Level 1 nested in repeated measures at Level 2 that are, in turn, nested in individuals at Level 3. To keep the model simple, only three covariates are included in the model: two individual characteristics (age and location of care) and time since diagnosis. In this analysis, the Rasch model orders the responses to a set of items (symptom presence or absence) according to a symptom's characteristic of prevalence in lieu of the traditional "item difficulty." The analog to the typical IRT latent ability is then a latent symptom experience.

Data and Participants

This example involves a secondary analysis of data from two descriptive longitudinal studies conducted from 1990 to 1998. There were 242 women from urban hospitals in the first study; 108 women from rural hospitals participated in the second study. These 350 women were newly diagnosed with breast cancer and undergoing chemotherapy. The participants were followed for 1 year and completed telephone interviews on four occasions. At each interview, the presence of 21 symptoms was recorded along with other characteristics.

Inclusion criteria for the primary studies required that women with breast cancer be at least 21 years of age; cognitively intact; and able to speak, read, and write English. Women under the care of a psychologist or psychiatrist, or with a diagnosed emotional or psychological disorder, were excluded. Nurse recruiters approached women who met the inclusion criteria, explained the studies, and obtained written consent. At mutually convenient times, the participants were interviewed by telephone; they also completed self-administered questionnaires. The ages of the participants

ranged from 28 to 98, with a mean of 67.72 years ($SD = 11.36$).

Measures

Symptoms were assessed using the self-report Physical Symptom Experience tool (Given et al., 1993). Participants responded regarding the presence of 21 symptoms commonly experienced by individuals with cancer, indicating whether they experienced the symptom (1) or not (0).

Time was coded in days since diagnosis. Demographic information included age and location of care. Location of care was coded rural = 1 if a rural hospital and rural = 0 if an urban hospital. To render the intercept of the regression line meaningful, age was grand-mean centered.

Analysis

Level 1 Model

The Level 1 model is a standard one-parameter item response or Rasch model, with random effects. In applying the Rasch model, item difficulty was used as symptom prevalence. Let $Y_{ijk} = 1$ if the symptom i was present at time j for person k and 0 otherwise. The probability of a symptom being present, Pr ($Y_{ijk} = 1$), is denoted by μ_{ijk}. At this level, there are 20 dummy variables, D_{mijk}, representing 20 of the 21 symptoms measured. So the Level 1 equation is

$$\log\left(\frac{\mu_{ijk}}{1 - \mu_{ijk}}\right) = \pi_{0jk} + \sum_{m=1}^{20} \pi_{mjk}D_{mijk} \qquad (1)$$

π_{mjk} is interpreted as the prevalence of the symptom m at time j for person k, compared with the reference symptom (i.e., the symptom for which a dummy variable was not included in the model). This model creates an interval scale for the symptoms, where large values of π_{mjk} indicate more prevalent symptoms while low values indicate less frequent symptoms. By IRT convention, the prevalence for the reference symptom (fatigue) is fixed at 0. This generates the IRT ordering of symptoms by prevalence.

The IRT latent variable describing aggregated symptoms is symptom experience, or π_{0jk}, which indicates the overall symptom experience at time j for person k. π_{0jk} becomes an outcome at Level 2, where the symptom experience trajectory is examined. Larger values of π_{0jk} indicate a higher relative prevalence of symptoms, while smaller values indicate a lower relative prevalence of symptoms.

Level 2 Model

The Level 2 model accounts for variation in symptom experience over time for each woman with breast cancer. Equation 2 models parameters from the Level 1 model, π_{0jk} and π_{mjk}. To conform to the Rasch methodology, we fixed the prevalence of each symptom (π_{mjk}) across time (Level 2) and individuals (Level 3) in the model. This constraint reflects the belief that, given a symptom experience, random samples of women with breast cancer will experi-

> *The simplest IRT model, the Rasch model, has only one parameter per item, namely difficulty.*

▼▼▼

ence a symptom with the same prevalence. Otherwise, the symptom may be regarded as biased against a subset of women with breast cancer. At Level 2, the symptom experience (π_{0jk}) is described as a function of time.

$$\pi_{0jk} = \beta_{00k} + \beta_{01k} \times \text{time}_{jk} + u_{0jk} \qquad (2)$$
$$\pi_{mjk} = \beta_{m0k}, \text{ for } m = 1, \ldots, 20$$

β_{00k} and β_{01k} represent the initial symptom experience, and the linear daily rate of change in symptom experience for individual k, respectively. The random effects, u_{0jk}, are the deviations at time j of individual k's symptom experience from the predicted. β_{m0k} represents the prevalence of the symptom m, compared with the reference symptom for individual k.

Level 3 Model

At Level 3, the symptom experience trajectory is explained using person-specific characteristics, such as age and location of care.

$$\beta_{00k} = \gamma_{00} + \gamma_{001} \times (\text{age}_k - 67.72)$$
$$\qquad + \gamma_{002} \times \text{rural}_k + \nu_{00k}$$
$$\beta_{01k} = \gamma_{010} + \gamma_{011} \times (\text{age}_k - 67.72) \qquad (3)$$
$$\qquad + \gamma_{012} \times \text{rural}_k + \nu_{01k}$$
$$\beta_{m0k} = \gamma_{m00}, \text{ for } m = 1, \ldots, 20$$

In this equation, γ_{000} is the expected initial symptom experience for women with breast cancer who are receiving care in urban hospitals; γ_{001} is the expected difference in the initial symptom experience between two women who differ by 1 year in age; γ_{002} is the expected difference in the average initial symptom experience between the rural and urban locations of care; γ_{010} is the expected average daily rate of change in symptom experience for women receiving care at the urban hospitals; γ_{011} is the difference in the expected daily rate of change in symptom experience between two women who differ by 1 year in age; γ_{012} is the difference in the expected daily rate of change in symptom experience between the rural and urban studies; and γ_{m00} is the prevalence of the symptom m compared with the reference symptom.

By combining the Levels 1, 2, and 3 models, the hierarchical generalized linear model can be estimated. The combined model tests how the log-odds of experiencing a symptom vary with time- and person-specific characteristics, such as age and location of care. This three-level hierarchical model can be viewed as an item–response model embedded within a hierarchical structure, in which repeated measures are nested within women with breast cancer.

Missing data were addressed by using complete case analyses (Little & Rubin, 2002); that is, if at least one symptom was recorded as present or absent during an interview, then this interview information was used in the analysis. The number of symptoms recorded (present or absent) during interviews ranged from 10 to 21. Some women had fewer than four interviews, resulting in 1,184 interviews (rather than $350 \times 4 = 1,400$) included at Level 2. Since every woman had at least one interview, and all women had both age and location of care recorded, 350 individuals were included in the analysis at Level 3.

TABLE 1. Raw Data Symptom Frequency (All Observations Combined)

Symptoms	Yes	No	Total	Yes (%)
Fatigue	693	491	1,184	58.53
Pain	462	722	1,184	39.02
Insomnia	426	758	1,184	35.98
Dry mouth	402	781	1,183	33.98
Loss of feeling	326	857	1,183	27.56
Urinary frequency	301	882	1,183	25.44
Weakness	289	894	1,183	24.43
Cough	262	921	1,183	22.15
Constipation	225	958	1,183	19.02
Nausea	208	975	1,183	17.58
Concentration	187	997	1,184	15.79
Poor appetite	182	1000	1,182	15.40
Shortness of breath	169	1015	1,184	14.27
Weight loss	161	1017	1,178	13.67
Coordination problems	103	1081	1,184	8.70
Diarrhea	102	1082	1,184	8.61
Mouth sores	66	1117	1,183	5.58
Difficulty swallowing	57	1124	1,181	4.83
Vomiting	46	1138	1,184	3.89
Fever	45	1138	1,183	3.80
Dehydration	26	1156	1,182	2.20

Note. Some of the 350 women had fewer than four interviews and the presence of fewer than 21 symptoms recorded at each interview resulting in 1,184 interviews and varying totals.

FIGURE 1. Symptom prevalences (γ_{m00}) according to the unconditional model.

We present two models, an unconditional and a conditional, estimated using HLM 6.20 (Raudenbush, Bryk, Cheong, & Congdon, 2004). The unconditional model has no covariates at Level 2 or 3, which yields a readily interpretable ordering of symptoms as well as the unadjusted symptom experience estimates for each person at each occasion that they recorded presence or absence of at least one symptom. We examined the symptom experience over time by testing linear and quadratic trajectories at Level 2. To test the associations between individual variables and symptom experience, these variables were incorporated into the multivariate model at Level 3. In the final model, Level 1 remains the same as in the unconditional model (see Equation 1), but now, entered into the model are the time-level variable (days since diagnosis) at Level 2, and the individual-level variable (age and location of care) at Level 3, as previously shown in Equations 2 and 3.

Model Results

Unconditional Model

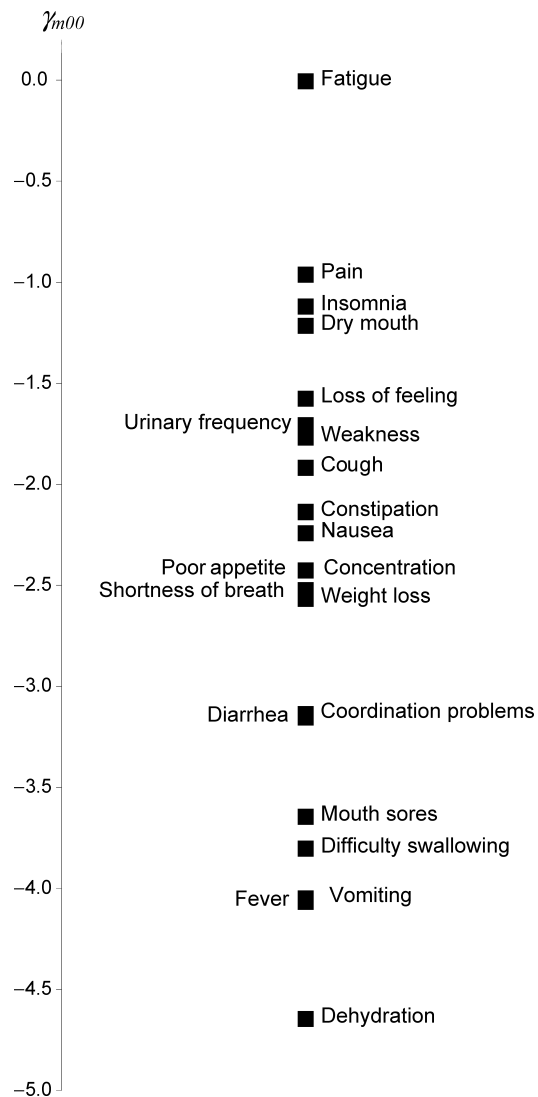Fatigue, the most common symptom in the raw data, was used as the reference symptom (Table 1). The results of the unconditional model yield a readily interpretable ordering of symptoms. Figure 1 shows the symptoms organized by their prevalence (γ_{m00}); the more prevalent symptoms appear at the top (high values), while the less prevalent appear at the bottom (low values). Symptoms appearing close together in Figure 1 have similar symptom prevalence. Construct validity for this scale was confirmed by the fact that pain and fatigue occurred with greatest frequency, which has been well-established in the cancer literature (Given, Given, Azzouz, Kozachik, & Stommel, 2001; Mock, 2003; Patrick et al., 2003). The lowest frequency symptom during chemotherapy treatment for breast cancer was dehydration (Table 1).

This model produced an unadjusted symptom experience estimate for each individual and each occasion when the presence of at least one symptom was recorded (Figure 2). These symptom experience estimates are approximately normally distributed and may be used as either a covariate or an outcome in other models.
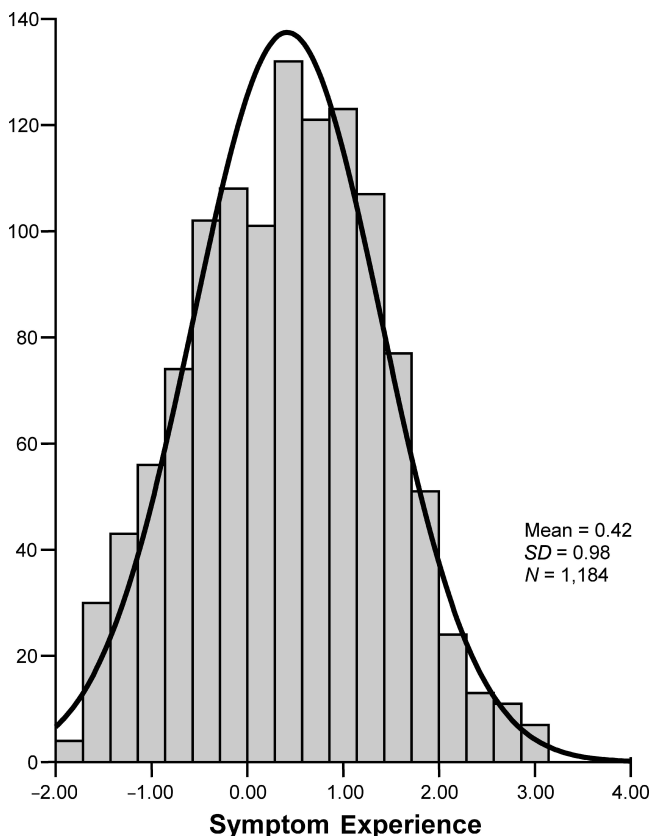
FIGURE 2. Histogram of symptom experience from the unconditional model, π_{0jk}. Some of the 350 women had fewer than four interviews, resulting in 1,184 total interviews.

Conditional Model

Since our focus was to determine the trajectory of symptom experience as well as its association with important individual variables, partial output for Levels 2 and 3 is reported in Table 2. Both the linear and quadratic trajectories were tested; however, the quadratic term did not significantly improve the model fit. Therefore, a linear trajectory was used in the final model. Time was significantly, negatively associated with symptom experience ($\hat{\gamma}_{010} = -.002$, $p < .001$). So, as women with breast cancer moved through the year, on average their symptom experience improved. Since we

TABLE 2. Partial Output of Estimates for the Conditional Model (Excluding Symptoms Prevalence)

Variable	Coefficient	Standard Error	p
Intercept, γ_{000}	.605	0.106	<.001
Age, γ_{001}	−.010	0.007	.173
Rural, γ_{002}	.268	0.185	.150
Time, γ_{010}	−.002	0.0003	<.001
Time × Age, γ_{011}	.00005	0.00003	.085
Time × Rural, γ_{012}	.0002	0.0007	.819

hypothesized that the symptom experience trajectory may differ according to women's age and location of care, age and rural were used to explain initial symptom experience and change in symptom experience. Neither age nor location of care was found to be statistically significantly associated with change of symptom experience over time ($p = .085$ and $p = .819$, respectively), nor were they found to be statistically significantly associated with symptom experience ($p = .173$ and $p = .150$, respectively; Table 2).

Discussion

The benefits of using IRT are illustrated by the results of the unconditional model. First, IRT created a meaningful metric that reflects the varying prevalence of symptoms in women with breast cancer (Figure 1), while reducing the skewness that commonly arises in composite measures of symptoms (Figures 2 and 3). Second, the analysis provided estimates of the latent symptom experience for each person at each occasion when the presence or absence of at least one symptom was recorded. These symptom experience estimates can be used as explanatory or outcome variables in other models.

Several of the numerous benefits of embedding IRT into an HLM framework were illustrated in the example above. First, this methodology provided a framework for incorporating repeated observations on the presence of
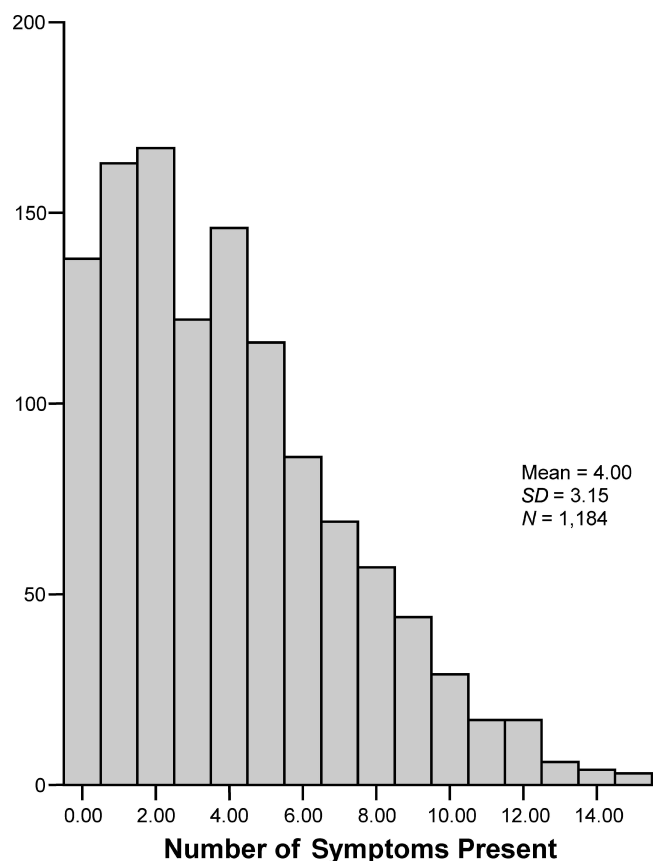

FIGURE 3. Histogram of total number of symptoms present. Some of the 350 women had fewer than four interviews, resulting in 1,184 total interviews.

symptoms to examine changes in the latent variable symptom experience over time. The results on the conditional model showed that the symptom experience of women with breast cancer improved over time. Second, this methodology allowed us to examine the relationship between individual variables and the latent symptom experience. Contrary to our hypothesis, controlling for the location of care, no statistically significant association of age with the symptom experience trajectory was found.

Moreover, the hierarchical framework provides a way to manage item nonresponse. Presently, two common approaches for combining symptom information use the sum or the proportion of the symptoms present. When using a summary score, a nursing researcher must make an arbitrary decision regarding how to handle item nonresponse. Using the sum assumes that everyone has the same number of symptoms recorded, but not necessarily present; the symptoms that are not recorded are assumed to be not present. The proportion approach assumes that each symptom contributes the same amount of information, which is again problematic, since some symptoms occur more frequently than others. A researcher can use an IRT model without having to decide what to do with missing data, as long as the data are assumed missing at random, a comparatively mild assumption (Little & Rubin, 2002).

The task of combining information from multiple-item responses arises frequently in studies of health outcomes. In many of these studies, the items are measured over time and nested within individuals, and item-level missing data are often unavoidable. This report demonstrates how embedding a Rasch model into HLM can address these research challenges. ▼

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Physical Functioning

Effect of Behavioral Intervention for Symptoms Among Individuals With Cancer

Ardith Doorenbos ▼ Barbara Given ▼ Charles Given ▼ Natalya Verbitsky

▶ **Background:** Individuals with cancer receiving chemotherapy suffer deterioration in physical functioning due to symptoms arising from the cancer disease process and its treatment.

▶ **Objectives:** To determine if age, chronic health conditions (comorbidity), stage of cancer, depressive symptomatology, symptom limitations, sex, and site of cancer moderate the effects of cognitive behavioral intervention on physical function and to determine if symptom limitations mediate the effect of the intervention on physical functioning.

▶ **Methods:** Two hundred thirty-seven individuals with solid tumor cancer (118 experimental and 119 control group) participated in this 10-contact, 18-week randomized control trial. Cognitive behavioral theory guided the nurse-delivered problem-solving experimental intervention. The control group received conventional care. Interviews occurred at baseline and 10, 20, and 32 weeks.

▶ **Results:** Women with breast cancer had significantly better physical functioning than women with lung cancer. Chronic health conditions, symptom limitation, and depressive symptomatology at baseline were found to moderate the effect of intervention on physical function. Symptom limitation, however, was not found to mediate the effect of intervention on physical functioning.

▶ **Discussion:** The intervention was shown to affect physical function trajectories differently for individuals with different personal and health characteristics. Because poor physical functioning is strongly associated with mortality and poor quality of life, this information may be used by health professionals to target interventions to those who might be most responsive.

▶ **Key Words:** depressive symptomatology · physical functioning · solid tumor cancer · symptoms

arising from both the disease process and its treatment (Patrick et al., 2003). It has been demonstrated that individuals with cancer who report more limitations from their symptoms also experience greater declines in physical functioning, reduced quality of life, and increased mortality (Dodd, Miaskowski, & Paul, 2001; Kurtz, Kurtz, Stommel, Given, & Given, 2001; Serlin, Mendoza, Nakamura, Edwards, & Cleeland, 1995). In response, there has been increased attention toward interventions targeting symptoms to reduce symptom-related negative consequences among individuals with cancer (Patrick et al., 2003).

The theoretical basis behind many behavioral interventions is cognitive behavioral theory. In this theory, behavioral change can occur with the acquisition of self-management knowledge, skills, and behaviors (Dobson, 2001; Given, Given, Champion, Kozachik, & DeVoss, 2003). The major premise of this theory is that providing interventions to individuals with cancer should increase their self-efficacy by developing skills through practice, observing others, and being verbally persuaded that the skill will be effective (Bandura, 1997). Enhancing an individual's self-efficacy should attenuate the probability of the individual experiencing emotional distress, functional impairment, treatment and disease-related symptoms, and decreased quality of life.

Research has shown behavioral interventions to be particularly efficacious among individuals with cancer. For example, a meta-analysis of 45 studies reporting 62 treatment control comparisons found that significant beneficial effect sizes were .24 for emotional measures, .19 for function measures, .26 for symptoms, and .28 for global measures (Meyer & Mark, 1995). In a meta-analysis of 116 studies, the significant beneficial effects of psychoeducational interventions were found for the outcomes of anxiety, depression, mood, nausea, vomiting, pain, and

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The American Cancer Society (2005) has identified that one out of four Americans is diagnosed with cancer at some point in life. Individuals with cancer who receive chemotherapy suffer many limitations due to symptoms

knowledge (Devine & Westlake, 1995). The meta-analyses of research studies using behavioral interventions highlight the efficacy of these interventions among individuals with cancer. However, few studies have examined the moderators and mediators that determine the conditions for which, or the individuals for whom, such interventions are most effective, nor have they examined how the interventions work.

Moderators specify for which individual or under what conditions an intervention is effective (Baron & Kenny, 1986). Thus, the intervention would be stronger or weaker at different levels of the moderator variables. In this paper, we examine if factors known to be associated with physical functioning—such as age, chronic health conditions, site and stage of cancer, symptoms, and depressive symptomatology (Given, Given, Azzouz, Stommel, & Kozachik, 2000; Kurtz et al., 1999, 2000; Patrick, Johnson, Goins, & Brown, 2004)—also moderate the effect of the intervention on physical functioning. For example, individuals who have lower depressive symptomatology (the moderator variable) may have a greater increase in physical function when receiving the intervention, but those with greater depressive symptomatology may not increase in physical function.

Tests for mediator effects are equally important in understanding the conditions under which interventions affect physical functioning. A mediator provides information about how or why two variables are related (Baron & Kenny, 1986; Dudley, Benuzillo, & Carrico, 2004). Exploring the relationships among medical conditions, symptoms, and functioning in older adults, for example, Bennett, Stewart, Kayser-Jones, and Glaser (2002) hypothesized that the adverse effect of the medical condition on physical functioning was mediated by symptom severity. They found that a significant portion of the relationship between medical conditions and physical functioning was explained by the symptoms of pain and fatigue. In a previous analysis, it was demonstrated that a cognitive behavioral intervention provided to individuals with cancer undergoing chemotherapy treatment was more effective than control in reducing symptom limitation (Doorenbos et al., 2005). Thus, it was hypothesized that the resulting decrease in symptom limitation from the intervention may mediate or explain how the intervention affects physical function.

Symptom limitation could have either a mediating or moderating influence on the relationship between our intervention and physical functioning. Symptom limitations could mediate the relationship between the intervention and physical functioning by indicating that the change in physical functioning due to the intervention is in part attributable to changes in symptom limitations. Alternatively, baseline symptom limitation could moderate the impact of the intervention on physical function; that is, individuals with cancer who have higher baseline symptom limitation are more (or less) able to benefit from an intervention's impact on physical function.

To explore potential moderators and mediators of the intervention on physical function, a secondary data analysis was conducted of the random control trial (RCT), in which cognitive behavioral theory guided the intervention.

The aims of this paper are (a) to determine if age, chronic health conditions, stage of cancer, symptom limitations, depressive symptomatology, sex, and site of cancer moderate the effects of intervention on physical functioning; and (b) to determine if symptom limitations mediate the effect of the intervention on physical functioning.

Methods

Eligibility Criteria and Settings

The primary RCT used for this secondary analysis was designed to examine both individuals with cancer and their caregivers. Thus, eligible participants were individuals newly diagnosed with solid tumor cancers, undergoing chemotherapy, and having a family caregiver; however, the data contributed by the caregivers were not used in this secondary analysis. The eligibility criteria and settings for the primary study are well documented in other publications (Doorenbos et al., 2005; Given et al., 2004a, 2004b).

Procedures

Human subjects approval was obtained from the institutional review boards at university and clinical settings. Recruitment and follow-up occurred in the years 1999 through 2001. Nurse recruiters identified 609 dyads who met the eligibility criteria. Two hundred sixty-three dyads agreed to participate in the study. Following the loss of 26 additional dyads between consent and completion of the baseline survey, 237 participants were randomized to either the experimental or the control condition, using the SAS minimization procedure. Figure 1 shows the attrition and retention by group. Analysis examining baseline equivalencies, using chi-square and t tests, revealed no significant differences between intervention and control groups at baseline. Between Weeks 20 and 32, more experimental group participants dropped out than during the same period in the control group; however, this trend towards significance had no discernable pattern.

Intervention

Cognitive behavioral theory guided the intervention provided in this RCT. The conceptual relevance of this intervention for individuals with cancer is linked to enhancing self-efficacy. The intervention goal was to provide empirically based strategies to enhance self-efficacy: self-care management information, counseling and support, and problem-solving and communication skills (Devine, 2003; Moore, Von Korff, Cherkin, Saunders, & Lorig, 2000; Oliver, Kravitz, Kaplan, & Meyers, 2001).

The intervention was delivered by trained nurses over the 10 contacts. Table 1 details the pattern and sequence of contacts, each approximately 45–60 minutes in length. The plan of care and intervention was collaboratively developed by the participant and the nurse intervener. The process of establishing and adapting the plan of care has been previously documented (Doorenbos et al., 2005; Given et al., 2004a, 2004b). The assessment of fidelity to intervention followed the recommended best practices for treatment fidelity (Bellg et al., 2004; Resnick et al., 2005).

Data Collection

Data collection occurred by trained telephone interviewers using a computer-assisted telephone interviewing system at baseline, Week 10 (midpoint of the intervention), Week 20 (immediately after conclusion of the intervention), and at Week 32 (for follow-up). Telephone interviews were used; the telephone interview approach has been shown to increase the amount and quality of data collected in multisite studies (Kornblith & Holland, 1996). The interviewers administered a structured survey consisting of self-report measures. The interview took approximately 1 hour to complete and included questions regarding symptoms, physical function, depressive symptomatology, and chronic health conditions. The interviewers were not blinded to study conditions.

Measures

The outcome, self-reported physical functioning, was measured by the 10-item, SF-36 physical functioning subscale (Ware, Snow, Kosinski, & Gandek, 1993). The items are rated on a 3-point Likert-type scale, summed, and then transformed to a 0–100 scale, with higher scores indicating better functioning. The psychometric properties of the SF-36 have been tested extensively in many groups of individuals with chronic illness, and the scales have demonstrated good reliability and validity (Ware & Gandek, 1998). In this study, the Cronbach's alpha reliabilities for the four time points of the study were .93, .91, .93, and .94, respectively.
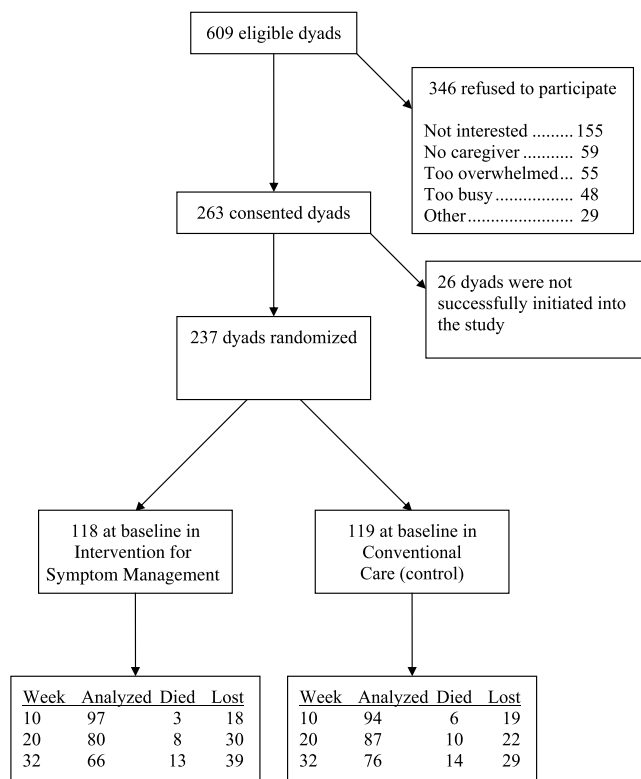
FIGURE 1. Study flow.

TABLE 1. Pattern and Sequence of Contacts for the Intervention Group

Week	1	3	5	7	9	11	13	15	17	19
Format	P	T	P	T	P	T	P	T	P	T

Note: T = telephone interview; P = personal interview.

Covariates included participant demographics, stage and site of cancer, symptom limitations, depressive symptomatology, and chronic health conditions. Demographics questions included sex, age, income, race, and marital status.

Participants' medical records were monitored during the study to obtain site and stage of cancer information. Cancer stage was coded as early (Stage 1 or 2) or late (Stage 3 or 4), according to the TNM staging criteria of the American Joint Committee on Cancer (2003). Cancer sites were combined into three groups: breast, lung, and other (which included colon, gynecological, lymphoma, pancreatic, and uterine cancers). As some cancers are sex specific, site and sex cancer categories were developed: male and female lung, male and female other, and female breast cancers. Appropriate dummy variables were created using lung and female as the reference category, because individuals with lung cancer were reported to experience less physical functioning than individuals with other sites of cancer (Cooley, 2000).

Symptom limitations were measured using the Symptom Experience Tool (Given et al., 1993). The presence of depressive symptomatology was assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). In this study, the Cronbach's alpha for baseline CES-D reliability was .81. Because we were interested in the potential moderation effect of depressive symptomatology on the intervention, only the baseline depressive symptomatology was used for analysis. Chronic health conditions were assessed using a modified version of the Comorbidity Questionnaire (Katz, Chang, Sangha, Fossel, & Bates, 1996). For the purposes of analysis, chronic health condition scores were divided into two groups: fewer than three chronic health conditions, and three or more chronic health conditions.

Analysis

The primary outcome for this study was the physical functioning subscale of the SF-36 measured at baseline and Weeks 10, 20, and 32. A two-level, hierarchical linear model (HLM) was used (Raudenbush & Bryk, 2002; Raudenbush, Bryk, Cheong, & Congdon, 2004). This model affords an integrated approach for studying the structure and predictors of individual change as well as providing the appropriate standard errors and correct statistical inferences (Raudenbush, 2001; Raudenbush & Bryk, 2002). Compared to the standard repeated measures analysis of variance (ANOVA) models, HLM models are more flexible. For example, they allow the use of data on individuals who are missing one or more observations,

where the assumption of missing at random holds (Little & Rubin, 2002).

The Level 1 model defines physical functioning trajectory within each individual over time. The Level 2 model examines the differences between these trajectories. Since at most four repeated measures were observed per person, a cubic is the highest order polynomial that can be fit to these data. The physical functioning trajectory was examined and the cubic order polynomial fit statistically significantly better than the quadratic (χ^2 = 9.844, df = 1, p = .002) or the linear (χ^2 = 23.171, df = 5, p = .001) polynomials. Thus, the unconditional model is

$$
\begin{aligned}
\text{Level 1:} \quad PF_{ti} = {} & \pi_{0i} + \pi_{1i} \, (Time - 5)_{ti} \\
& + \pi_{2i} \, (Time - 5)_{ti}^2 + \pi_{3i} \, (Time - 5)_{ti}^3 \\
& + e_{ti} \quad\quad (1)
\end{aligned}
$$

$$
\begin{aligned}
\text{Level 2:} \quad & \pi_{0i} = \beta_{00} + r_{0i} \\
& \pi_{1i} = \beta_{10} + r_{1i} \\
& \pi_{2i} = \beta_{20} + r_{2i} \\
& \pi_{3i} = \beta_{30} \quad\quad (2)
\end{aligned}
$$

for i = 1, 2,…, n participants and t = 0, 1, 2, 3 interview occasions. Time was coded as time since the start of the study in months; it is centered at 5 months (or 20 weeks) because this was the first postintervention observation. So, π_{0i} is the expected physical functioning of participant i at Week 20; π_{1i} is the expected instantaneous rate of change in physical functioning of participant i at Week 20; π_{2i} is the expected acceleration (or change in the rate of change) in physical functioning for participant i at Week 20; and π_{3i} is the expected change in acceleration in physical functioning for participant i. Note that a cubic growth trajectory implies that growth and acceleration rates may change over time for a given individual. βs are the corresponding expected average population estimators.

The first aim of this study was to explore if other factors known to be associated with physical functioning moderate the effects of intervention (CBI) on physical functioning. Thus, the Level 1 model stays the same as in Equation 1. Age (age 60), chronic health conditions (chronic_high, with chronic_low category as the reference), site and stage of cancer (lung_male, breast_female, other_male, and other_female, with lung_female category as the reference), stage of cancer (late-stage, with early-stage as reference category), baseline symptom limitations (sym_lim-22), and depressive symptomatology (depr-16) were entered in each of the four equations at Level 2, along with the intervention group and its interactions with the covariates. Note that continuous variables were centered to make the intercept more readily interpretable. Age and symptom limitation were grand-mean centered (around their respective means of 60 and 22), and depression was centered at 16 (as a score of 16 or higher on the CES-D is indicative of clinical depression; Radloff, 1977). More-

over, a quadratic effect of age and its interaction with intervention group were also included in the initial model to test for a nonlinear relationship between age and physical functioning.

A more parsimonious model was discovered by removing variables found to be associated insignificantly with physical function. The quadratic effect of age and late stage, and their interactions with intervention, were removed from all four Level 2 equations. Furthermore, site and gender covariates and their interactions with intervention were removed from all but the intercept (π_{0i}) equation. Model deviances were compared using a chi-squared test (χ^2 = 65.27, df = 48, p = .05), and the more parsimonious model was found not to be significantly different from the original model. Controlling for other covariates, age and its interaction with intervention were not significant in the final model; however, the deviance comparison test of the full model to the model without age yielded a significant chi-square statistic (χ^2 = 80.15, df = 56, p = .02). Therefore, although age was not associated significantly with physical function in the final model, based on the significant chi-square statistic it was retained in the final model. Thus, the final Level 1 model stays the same as in Equation 1, whereas the Level 2 final model can be seen in Appendix A.

The second aim of this study was to examine if symptom limitations mediate the effect of the intervention on physical functioning. This was tested using Baron and Kenny's (1986) criteria, in which three models are examined. Methodology for examining mediational effects in cross-sectional multilevel settings has been discussed elsewhere (Kenny, Korchmaros, & Bolger, 2003; Krull & MacKinnon, 2001; Raudenbush & Sampson, 1999). However, in this study the focus is on examining upper-level mediating effects: that is, the causal variable (CBI) whose effect is mediated is a Level 2 variable (Kenny et al., 2003) in a longitudinal setting.

First, a model looking at the overall (direct and indirect) association between intervention and outcome (physical functioning) was considered by including the intervention variable at Level 2. The Level 1 equation stays the same as in Equation 1, whereas the Level 2 equation is:

$$
\begin{aligned}
\text{Level 2:} \quad & \pi_{0i} = \beta_{00} + \beta_{01} CBI_i + r_{0i} \\
& \pi_{1i} = \beta_{10} + \beta_{11} CBI_i + r_{1i} \\
& \pi_{2i} = \beta_{20} + \beta_{21} CBI_i + r_{2i} \\
& \pi_{3i} = \beta_{30} + \beta_{31} CBI_i \quad\quad (3)
\end{aligned}
$$

The four CBI coefficients (β_{01}, β_{11}, β_{21}, β_{31}) represent the overall effect of the intervention on physical functioning trajectory. Note that mediator effects should only be tested if there is a significant association between the intervention and the outcome variable (Bennett, 2000); that is, a significant effect of intervention on physical function trajectory in the first model.

The second model looks at the direct effect of intervention controlling for the mediator (symptom limitations). To ensure the proper temporal causal sequence of variables, a lagged symptom limitation is included in the model at Level 1; symptom limitation at time $t - 1$ (Sym_Lim$_{t-1,i}$) is used to predict physical functioning at time t (PF$_{ti}$). Because symptom limitation was not recorded prior to baseline physical functioning, at most three interview occasions could be used per individual. Thus, a quadratic trajectory for physical functioning is examined. The model is:

Level 1:
$$PF_{ti} = \pi_{0i} + \pi_{1i}\,(Time - 5)_{ti} + \pi_{2i}\,(Time - 5)^2_{ti} + \pi_{3i}\,(Sym\_Lim)_{t-1,i} + e_{ti}$$

Level 2:
$$\pi_{0i} = \beta_{00} + \beta_{01}CBI_i + r_{0i}$$
$$\pi_{1i} = \beta_{10} + \beta_{11}CBI_i + r_{1i}$$
$$\pi_{2i} = \beta_{20} + \beta_{21}CBI_i$$
$$\pi_{3i} = \beta_{30} \qquad (4)$$

for $i = 1, 2,..., n$ participants and $t = 1, 2, 3$ interview occasions. In this model, the three CBI coefficients (β_{01}, β_{11}, β_{21}) represent the effect of CBI not attributable to symptom limitation.

The last of the three mediation models examines the effect of the intervention on the mediator (symptom limitation). This is shown in Equation 5 below:

Level 1:
$$Sym\_Lim_{ti} = \pi_{0i} + \pi_{1i}\,(Time - 5)_{ti} + \pi_{2i}\,(Time - 5)^2_{ti} + \pi_{3i}\,(Time - 5)^3_{ti} + e_{ti}$$

Level 2:
$$\pi_{0i} = \beta_{00} + \beta_{01}CBI_i + r_{0i}$$
$$\pi_{1i} = \beta_{10} + \beta_{11}CBI_i + r_{1i}$$
$$\pi_{2i} = \beta_{20} + \beta_{21}CBI_i + r_{2i}$$
$$\pi_{3i} = \beta_{30} + \beta_{31}CBI_i \qquad (5)$$

where $i = 1, 2,..., n$ participants and $t = 0, 1, 2, 3$ interview occasions. In this model the four CBI coefficients (β_{01}, β_{11}, β_{21}, β_{31}) represent the effect of the intervention on the mediator trajectory.

Results

Baseline demographic and clinical characteristics by group are presented in Table 2. Participants ranged in age from 31 to 87 years, with a mean age of 60 years ($SD = 10$ years). The majority of the participants were married (75%), White (90%), and female (74%). Fifty-four percent of participants came from households with annual incomes over $60,000. Sixty-seven percent of the participants had late-stage (Stage 3 or 4) cancer. The most common site of cancer was breast (38%), followed by lung (35%). Baseline

TABLE 2. Baseline Demographics and Clinical Characteristics by Group

Variable	Intervention group ($n = 118$), n (%)	Control group ($n = 119$), n (%)
Race/ethnicity		
White	108 (90%)	108 (90%)
Other	10 (10%)	11 (10%)
Sex		
Female	86 (73%)	88 (74%)
Male	32 (27%)	31 (26%)
Marital status		
Never married	2 (1.5%)	8 (7%)
Married	89 (76%)	86 (73%)
Divorced/separated	18 (15%)	12 (10%)
Widowed	9 (7.5%)	12 (10%)
Income (US $)		
0–59,000	40 (46%)	44 (47%)
60,000+	47 (54%)	51 (53%)
Stage of cancer		
Early	40 (33%)	38 (32%)
Late	78 (67%)	81 (68%)
Site of cancer		
Breast	47 (39%)	46 (38%)
Lung	40 (35%)	41 (35%)
Other	31 (26%)	32 (27%)
	Mean (*SD*), min–max	Mean (*SD*), min–max
Age (years)	60.4 (9.7), 36–83	58.7 (11.1), 31–87
CES-D	12.1 (9.1), 0–38	13.5 (9.1), 0–44
Chronic health conditions	2.3 (1.6), 0–7	2 (1.7), 0–7
Symptom limitations	23.3 (21.9), 0–91	21 (17.6), 0–90
Physical functioning	65 (28.6), 0–100	63 (29.9), 0–100

CES-D scores ranged from 0 to 44, with a mean of 12.78 (9.1). Thirty-two percent of the participants had a score of 16 or greater on the CES-D. (The score on the CES-D indicative of clinical depression is 16.) Descriptive statistics for continuous variables across all time point are presented in Table 3.

Results for Aim 1

Aim 1 (Table 4) was to determine if age, chronic health conditions, stage of cancer, depressive symptomatology, symptom limitation, sex, and site of cancer moderate the effect of intervention on physical functioning. Controlling for other covariates, the expected difference in physical functioning at 20 weeks between individuals with low chronic health conditions in the intervention and the

TABLE 3. Descriptive Statistics for Continuous Variables Across Time Points

	n	Minimum	Maximum	Mean	SD
Baseline					
Physical function	237	0	100	64.18	29.45
Symptom limitation	237	0	91	22.24	19.79
CES-D	228	0	44	12.78	9.04
Week 10					
Physical function	191	0	100	64.36	26.87
Symptom limitation	186	0	85	20.19	17.20
CES-D	179	0	38	11.45	8.97
Week 20					
Physical function	167	5	100	70.64	28.11
Symptom limitation	137	0	61	12.68	14.83
CES-D	151	0	39	8.48	8.81
Week 32					
Physical function	142	5	100	72.74	28.58
Symptom limitation	113	0	78	12.43	14.89
CES-D	129	0	31	7.64	7.43

Note. CES-D = Center for Epidemilogic Studies Depression Scale.

control groups is 7.69 (β_{01}) and the expected difference for those with high chronic health conditions is 22.97 ($\beta_{01} + \beta_{05}$). Thus, controlling for other covariates, CBI intervention may work better at Week 20 for individuals with a higher number of chronic health conditions than for individuals with low chronic health conditions (β_{05} = 15.287, p = .069). Furthermore, the difference in the intervention effects on physical functioning between the two groups (individuals with high and low chronic health conditions) is statistically significantly different in the instantaneous rates of change at 20 weeks (β_{15} = 5.757, p = .021). In other words, the intervention benefited the rates of change in physical functioning of individuals with high numbers of chronic health conditions more than those with low numbers of chronic health conditions at Week 20. Furthermore, the intervention effect on the change in acceleration between the high and low chronic conditions groups is also different (β_{35} = −0.39, p = .03). Thus, the expected trajectory of physical function is different between individuals within chronic health conditions by intervention status strata (Figure 2). This indicates that the number of chronic health conditions at baseline has a moderating effect on the effect of the intervention of physical function.

Controlling for other covariates, the effect of intervention similarly varies according to an individual's baseline depressive symptomatology at Week 20 (β_{07} = 1.05, p = .04). However, among individuals with higher levels of depressive symptomatology, the intervention effect on the curvature of the physical functioning trajectory at Week 20 was more negative than that of individuals with lower depressive symptomatology (β_{27} = −0.13, p < .01).

Similarly, the intervention effect on the change in curvature of the physical functioning trajectory for individuals with higher depressive symptomatology was more negative than for individuals with lower depressive symptomatology (β_{37} = −0.03, p < .01) over all time points. Thus, individuals with a score of 16 on the CES-D receiving intervention improved less in physical function than those with lower depressive symptomatology in the intervention group.

Controlling for other covariates, the effect of intervention on physical function also varies according to an individual's baseline symptom limitations. Individuals with higher symptom limitations at baseline respond to the intervention at Week 20 less than do those with lower symptom limitations at baseline (β_{09} = −0.67, p = .01). Moreover, the intervention has a more negative effect on the rate of change of physical functioning at Week 20 for individuals with higher baseline symptom limitations than it does for those with lower baseline symptom limitations (β_{19} = −0.18, p = .02). However, the intervention has a more positive effect on the expected curvature or acceleration at Week 20 and the overall change in curvature or acceleration for individuals with higher symptom limitations at baseline than for individuals with lower symptom limitations at baseline (β_{29} = 0.06, p < .01 and β_{39} = 0.02, p = .01, respectively). Thus, individuals with higher symptom limitations at baseline in the intervention group benefited more from the intervention than did those with lower symptom limitations receiving intervention.

Finally, no moderating effect of intervention by age (β_{03} = −0.086, p = .827, β_{13} = −0.079, p = .478, β_{23} = 0.022, p = .492, β_{33} = 0.007, p = .407) or by site and gender (β_{011} = −17.523, p = .062, β_{013} = −4.126, p = .590, β_{015} = 3.729, p = .675, β_{017} = 6.964, p = .675) was found. However, females with breast cancer experienced higher levels of physical functioning than females with lung cancer (β_{012} = 18.069, p = .001), and males with lung cancer experienced higher physical functioning than females with lung cancer (β_{010} = 15.708, p = .022).

Results for Aim 2

Aim 2 was to determine if symptom limitations mediate the effect of the intervention on physical functioning. Because there was no overall (direct or indirect) effect of the intervention on physical functioning detected (χ^2 = 1.66, df = 4, p > .5) using the first mediation model (Equation 3), further testing of the mediation effect (using the latter two models) did not occur.

Discussion

There is ample evidence of the effectiveness of interventions guided by cognitive behavioral theory. However, there is less evidence of moderators and mediators of intervention on outcomes available to inform the next generation of RCTs and guide clinical applications of interventions. To aid in alleviating this deficit, this study explored factors that were hypothesized to moderate and mediate the effect of a cognitive behavioral intervention on physical function among individuals with cancer.

As physical functioning is known to vary by age and stage and site of cancer, these variables were hypothesized

TABLE 4. HLM Final Estimation of Fixed Effects: Testing Moderators of Physical Functioning

Expected status at Week 20, π_{0j}	Coefficient	SE	p
β_{00} Intercept	55.460	5.519	.000***
β_{01} Intervention	7.686	8.018	.339
β_{02} Age	−0.325	0.268	.227
β_{03} Intervention × Age	−0.086	0.394	.827
β_{04} Chronic health condition	−15.428	6.227	.014**
β_{05} Intervention × Chronic health condition	15.287	8.370	.069*
β_{06} Depression	−1.300	0.358	.001***
β_{07} Intervention × Depression	1.052	0.511	.041**
β_{08} Symptom limitations	0.107	0.200	.595
β_{09} Intervention × Symptom limitations	−0.667	0.261	.012**
β_{010} Male lung cancer	15.708	6.790	.022**
β_{011} Intervention × Male lung cancer	−17.523	9.347	.062*
β_{012} Female breast cancer	18.069	5.461	.001*
β_{013} Intervention × Female breast cancer	−4.126	7.663	.590
β_{014} Female other cancer	8.106	6.355	.204
β_{015} Intervention × Female other cancer	3.729	8.888	.675
β_{016} Male other cancer	12.787	9.104	.162
β_{017} Intervention × Male other cancer	6.964	11.923	.559

Note: β_{00} intercept = expected physical functioning status at Week 20 for a female with lung cancer in the nonintervention group, with age = 60, low chronic conditions, depressive symptomatology = 16, and symptom limitations = 22.

Linear-expected change at Week 20, π_{1j}	Coefficient	SE	p
β_{10} Time	2.348	1.017	.022**
β_{11} Time × Intervention	−1.025	1.528	.503
β_{12} Time × Age	−0.032	0.075	.668
β_{13} Time × Intervention × Age	−0.079	0.112	.478
β_{14} Time × Chronic health condition	−2.095	1.827	.254
β_{15} Time × Intervention × Chronic health condition	5.757	2.477	.021**
β_{16} Time × Depression	−0.175	0.110	.114
β_{17} Time × Intervention × Depression	0.261	0.155	.094*
β_{18} Time × Symptom limitation	0.070	0.059	.241
β_{19} Time × Intervention × Symptom limitation	−0.179	0.079	.024**

Note: β_{10} Time is the expected change in physical functioning at Week 20 for an individual with cancer in the nonintervention group, with age = 60, low chronic conditions, depressive symptomatology = 16, and symptom limitations = 22.

TABLE 4. (continued)

Quadratic-expected acceleration or change in slope at Week 20, π_{2j}	Coefficient	SE	p
β_{20} Time²	−0.433	0.291	.139
β_{21} Time² × Intervention	−0.142	0.442	.749
β_{22} Time² × Age	−0.026	0.022	.233
β_{23} Time² × Intervention × Age	0.022	0.032	.492
β_{24} Time² × Chronic health condition	1.085	0.529	.041**
β_{25} Time² × Intervention × chronic health condition	−1.187	0.718	.100
β_{26} Time² × Depression	0.076	0.031	.015**
β_{27} Time² × Intervention × Depression	−0.125	0.045	.006***
β_{28} Time² × Symptom limitation	−0.034	0.017	.045**
β_{29} Time² × Intervention × Symptom limitation	0.063	0.023	.008***

Note: β_{20} Time² is the expected deceleration in physical functioning at Week 20 for an individual with cancer in the nonintervention group, with age = 60, low chronic conditions, depressive symptomatology = 16, and symptom limitations = 22.

Cubic-expected change in acceleration over all time points, π_{3j}	Coefficient	SE	p
β_{30} Time³	−0.153	0.076	.044**
β_{31} Time³ × Intervention	0.021	0.114	.854
β_{32} Time³ × Age	−0.002	0.006	.613
β_{33} Time³ × Intervention × Age	0.007	0.008	.407
β_{34} Time³ × Chronic health condition	0.236	0.136	.083*
β_{35} Time³ × Intervention × Chronic health condition	−0.393	0.185	.034**
β_{36} Time³ × Depression	0.016	0.008	.044**
β_{37} Time³ × Intervention × Depression	−0.031	0.012	.009***
β_{38} Time³ × Symptom limitation	−0.003	0.004	.438
β_{39} Time³ × Intervention × Symptom limitation	0.015	0.006	.011**

Note: β_{30} Time³ is the expected change in deceleration of physical functioning for an individual with cancer in the nonintervention group, with age = 60, low chronic conditions, depressive symptomatology = 16, and symptom limitations = 22.

Note: *p < .1; **p < .05; ***p < .01.

to moderate the association between intervention and physical function. Additionally, as some cancers, such as breast cancer, are sex-specific, sex by site variables were tested. Physical functioning varies significantly according to cancer site; lower levels of physical functioning at 20
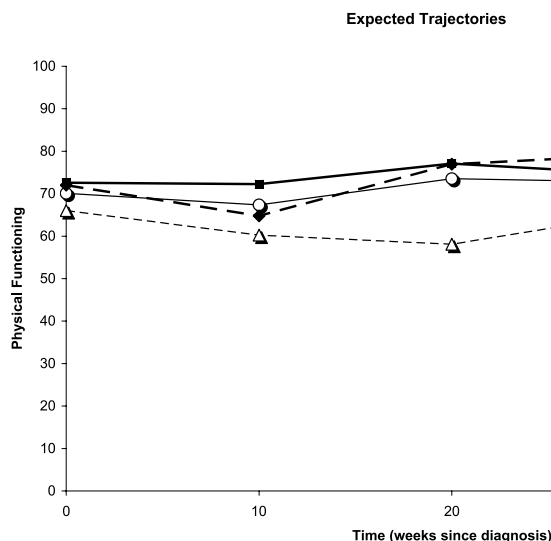
Expected Trajectories

FIGURE 2. Physical functioning trajectories by number of chronic health conditions and treatment group. —○— control, chronic low; — △ — control, chronic high; ▬■▬ trt, chronic low; ◆ ▬ trt, chronic high.

weeks are observed for women with lung cancer. Controlling for other covariates at 20 weeks, women with breast cancer had an average score of 73 on the SF-36 physical function subscale, compared to an average physical function score of 55 for women with lung cancer. This finding was in agreement with the findings of Kurtz et al. (1999). Significant differences were also seen within site by sex as with males and females with lung cancer in the current study. However, sex by site of cancer was not found to moderate the effect of the intervention effect on physical functioning. Additionally, an individual's age and stage of cancer were not found to moderate the effect of intervention on physical function.

Consistent with earlier work by our research team (Given et al., 2000), having three or more chronic health conditions was associated with lower physical functioning at Week 20. The results of this study indicate that the intervention had a greater impact at 20 weeks on participants with three or more chronic health conditions compared to those with two or fewer chronic health conditions. Thus, although the number of chronic health conditions cannot be changed, this intervention was particularly effective among those who were perhaps at greater risk of lower physical functioning.

The study results support and extend other research findings that suggest a strong relationship between depressive symptomatology at baseline and subsequent physical functioning (Patrick et al., 2004). This study provides further evidence that depressive symptomatology has a notable impact on physical functioning. At all time points, individuals with higher depressive symptomatology had lower physical functioning than did those with lower depressive symptomatology. This study's findings suggest that efforts should be made to identify and treat individuals with cancer who have high depressive symptomatology upon diagnosis or initiation of cancer treatment. If depressive symptomatology is treated, individuals with cancer may improve in physical functioning. Additionally, without corresponding improvement in depression, it is unlikely that individuals with higher depressive symptomatology will respond significantly to cognitive behavioral

interventions intended to improve physical functioning during their cancer experience.

Consistent with other research (Dodd et al., 2001; Kurtz et al., 2001; Serlin et al., 1995), this research supports findings of increasing symptoms being associated with decreased functional status in individuals with cancer. This research also supports that baseline symptom limitation levels moderate the effects of the intervention on physical function. As individuals with higher symptom limitation in the intervention group move through the cancer treatment experience, their physical functioning improves quickly, and at the end of the study they had greater improvement in physical functioning compared to those who entered the study with lower symptom limitations.

The results of this study did not support the hypothesis that symptom limitation would mediate the effect of intervention on physical function. According to cognitive behavioral theory, providing interventions to individuals with cancer should increase their self-efficacy by providing empirically based strategies to develop skills. This analysis did not consider the strategies provided by intervention nurses, nor the skills or amount of self-efficacy acquired by participants. Thus, it is possible that some strategies to enhance self-efficacy have different effects on physical functioning. It is also possible that the individuals receiving the intervention had varying degrees of skill acquisition. As this study conceptualized, rather than operationalized self-efficacy, future studies are needed that operationalize self-efficacy to better test the theoretical assumptions of the cognitive behavioral theory.

Symptom limitations explained about 30% of the variance in physical functioning after adjusting for time. Therefore, although there was a significant effect of the intervention on symptom limitations (Doorenbos et al., 2005), there would need to be a larger effect of symptom limitations, a larger direct effect of the intervention on physical functioning, or a higher power derived from a larger sample size, before a statistically verifiable effect of intervention on physical functioning could be established by the study. As the RCT was powered to examine the

effect of the intervention on symptom severity (Given et al., 2004a), it is possible there was insufficient power to determine the hypothesized mediation. Another study designed to test this effect specifically may be appropriate.

Another issue that might have influenced the non-significant results in the area of mediation is the possibility that the symptom limitation measure did not have adequate sensitivity. The study relied on a summary score of symptom limitations; it is possible that limitations of some symptoms have different effects on physical functioning. Increasing pain has been clearly linked in longitudinal studies with decreasing physical function (Williamson & Schulz, 1995); however, the association between other symptoms and physical function may be less strong. Additional research with larger numbers of participants experiencing each symptom would assist in clarifying the potential differential effect of particular symptoms on physical functioning.

As physical function had far less variability than symptom limitation, any effects of the intervention are less visible. This holds true for the direct effect of the intervention on physical function as well as any effects mediated by physical function. Physical function was constrained by a ceiling effect, whereas symptom limitation was not; thus, the relative insensitivity of physical function may have obscured a possible significant association.

Measures used in this study were based on participant self-reports. It is possible that individuals with depressive symptomatology systematically report their physical functioning to be worse than it actually is. This may, in part, explain the lower reported physical functioning among respondents with high depressive symptomatology.

Clinical and Research Implications

The interaction effects of interventions with chronic health conditions, symptom limitation, and depressive symptomatology provide nurse researchers with additional information to help clarify the choice of inclusion and exclusion criteria. Stratification to maximize power in subsequent RCTs can be based on the knowledge that individuals with varying chronic health conditions, symptom limitations, and depressive symptomatology at baseline have differential responses to the intervention. For nurse clinicians, information on moderators can help tailor interventions to a profile of individuals with cancer entering into a chemotherapy regimen at elevated risk of poor physical functioning. As lower physical functioning has been linked with increased mortality, interventions initiated at diagnosis or start of cancer treatment may improve poor physical functioning, possibly having an effect on mortality and certainly improving quality of life. ▼

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Appendix A

Level 2:

$$\pi_{0i} = \beta_{00} + \beta_{01}\,(CBI)_i + \beta_{02}\,(Age-60)_i$$
$$+ \beta_{03}\,(CBI)_i*(Age-60)_i + \beta_{04}\,(Chonic\_high)_i$$
$$+ \beta_{05}\,(CBI)_i*(Chronic\_high)_i + \beta_{06}\,(Depr-16)_i$$
$$+ \beta_{07}\,(CBI)_i*(Depr-16)_i + \beta_{08}\,(Sym\_lim-22)_i$$
$$+ \beta_{09}\,(CBI)_i*(Sym\_lim-22)_i$$
$$+ \beta_{010}\,(Lung\_male)_i + \beta_{011}\,(CBI)_i*(Lung\_male)_i$$
$$+ \beta_{012}\,(Breast\_fem)_i + \beta_{013}\,(CBI)_i*(Breast\_fem)_i$$
$$+ \beta_{014}\,(Other\_fem)_i + \beta_{015}\,(CBI)_i*(Other\_fem)_i$$
$$+ \beta_{016}\,(Other\_male)_i$$
$$+ \beta_{017}\,(CBI)_i*(Other\_male)_i + r_{0i}$$

$$\pi_{1i} = \beta_{10} + \beta_{11}\,(CBI)_i + \beta_{12}\,(Age-60)_i$$
$$+ \beta_{13}\,(CBI)_i*(Age-60)_i + \beta_{14}\,(Chonic\_high)_i$$
$$+\beta_{15}\,(CBI)_i*\,(Chronic\_high)_i + \beta_{16}\,(Depr-16)_i$$
$$+ \beta_{17}\,(CBI)_i*(Depr-16)_i + \beta_{18}\,(Sym\_lim-22)_i$$
$$+\beta_{19}\,(CBI)_i*\,(Sym\_lim-22)_i + r_{1i}$$

$$\pi_{2i} = \beta_{20} + \beta_{21}\,(CBI)_i + \beta_{22}\,(Age-60)_i$$
$$+ \beta_{23}\,(CBI)_i*(Age-60)_i + \beta_{24}\,(Chonic\_high)_i$$
$$+ \beta_{25}\,(CBI)_i*(Chronic\_high)_i$$
$$+ \beta_{26}\,(Depr-16)_i + \beta_{27}\,(CBI)_i*(Depr-16)_i$$
$$+ \beta_{28}\,(Sym\_lim-22)_i$$
$$+ \beta_{29}\,(CBI)_i*(Sym\_lim-22)_i + r_{2i}$$

$$\pi_{3i} = \beta_{30} + \beta_{31}\,(CBI)_i + \beta_{32}\,(Age-60)_i$$
$$+ \beta_{33}\,(CBI)_i*(Age-60)_i + \beta_{34}\,(Chonic\_high)_i$$
$$+ \beta_{35}\,(CBI)_i*(Chronic\_high)_i + \beta_{36}\,(Depr-16)_i$$
$$+ \beta_{37}(CBI)_i*(Depr-16)_i + \beta_{38}\,(Sym\_lim-22)_i$$
$$+ \beta_{39}\,(CBI)_i*(Sym\_lim-22)_i$$

TITLE

Symptom experience in the last year of life among individuals with cancer

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Abstract

Individuals with cancer often experience many symptoms that impair their quality of life at end of life. This study examines symptom experience at end of life among individuals with cancer, and determines if symptom experience changes with proximity to death, or differs by depressive symptomatology, sex, site of cancer, or age. A secondary analysis of data from three prospective, descriptive, longitudinal studies (N = 174) was performed, using a three-level hierarchical linear model. Fatigue, weakness, pain, shortness of breath, and cough were the five most prevalent symptoms in the last year of life. The symptom experience in the last year of life was significantly associated with site of cancer, depressive symptomatology, dependencies in activities of daily living, and independent activities of daily living at the start of the study. These findings shed light on the symptom experience in the last year of life for individuals with cancer. With greater understanding of the symptom experience, intervention strategies can be targeted to achieve the desired outcome of increased quality of life at end of life.

Keywords: end-of-life, symptoms, cancer, hierarchical linear modeling, depression, activities of daily living

Symptoms at End of Life among Individuals with Cancer

As cancer is one of the leading causes of death among Americans (1), it is important to understand the symptom experience among individuals with cancer approaching end of life. Individuals with cancer often suffer from many symptoms that impair their quality of life at end of life (2). Correspondingly, one goal of palliative end-of-life care is to provide symptom management; however, symptoms have been reported as poorly managed at the end of life (3). This inability to manage symptoms at the end of life may be due in part to a limited understanding of symptoms and the factors that are associated with symptoms at the end of life.

Improvements in symptom management techniques have been hampered by a dominant research focus on a single symptom (4). Symptoms, however, do not occur in isolation; rather, individuals with cancer have multiple, coexisting symptoms. To better understand the experience at end of life, a more complete picture of the symptom experience needs to be assessed, which in turn requires appropriate statistical methodology.

Current understanding of symptom experience at end of life derives from studies recruiting individuals with cancer, designated as terminally ill, having a prognosis of less than six months, and receiving hospice or palliative care (5,6,7). Recruitment of terminally ill individuals with cancer has given us great insight into the symptom experience at end of life; however, the current focus on individuals designated as terminally ill and receiving hospice or palliative care provides only a partial understanding of the symptom experience at end of life among individuals with cancer. The results of extant studies can neither be generalized to those whose terminal illness is

either unrecognized or unacknowledged, nor to those whose response to a terminal prognosis involves non-palliative, non-hospice approaches.

Furthermore, methods for the collection of symptom experience data at end of life have included proxy and retrospective interviews with caregivers. Proxy interviews are administered to caregivers of individuals nearing end of life, to relieve the respondent burden for those who are terminally ill (8,9). Proxy reports have been shown to be quite accurate for observable symptoms such as vomiting; however, the agreement between self and proxy reporting has been shown to be unreliable for symptoms that are less observable, such as pain or depression (8). Retrospective interviews with caregivers of the deceased individuals with cancer also have been used to understand the symptom experience at end of life (10), but the use of retrospective interviews may be subject to a significant recall bias. Thus, the use of proxy or retrospective interviews may not provide the most accurate understanding of the symptom experience at end of life.

In prior research (involving 1,000 individuals having advanced cancer upon initial referral to a Palliative Medicine Program), age, sex, and ADL/IADLs were related to symptom experience (12). Previous research has also found a relationship between depression and symptom severity (13). Additionally, certain sites of cancer are known to have a shorter life expectancy than others, for example, lung cancer compared to breast cancer (1). The shorter life expectancy may relate to higher symptom experience in the last year of life.

Prior research is lacking information on how symptom experience changes in the last year of life among individuals with cancer who are not enrolled in a specialized palliative care or hospice setting. As death approaches, the symptom experience may

evolve differently for each individual with cancer, and may be related to personal and health/illness characteristics (such as age, sex, ADL/IADLs, depression, and site of cancer).

This paper examines the symptom experience trajectory during the last year of life among individuals with cancer and whether it differs by depressive symptomatology, dependencies in activities of daily living (ADL), instrumental activities of daily living (IADL), sex, site of cancer, or age. Participants were enrolled in one of three longitudinal studies and were asked to respond to a common list of 21 symptoms. This exploration extends our understanding of the symptom experience at end of life in several important ways. First, the method of data collection is patient self-report. Second, the study focuses on a sample of individuals with cancer, who were followed prospectively, were receiving chemotherapy, and were not enrolled in hospice. Finally, it recognizes the importance of looking at a multiplicity of symptoms at end of life. Thus, this paper, by taking a prospective view of symptoms, provides a different picture of the symptom experience at end of life among individuals with cancer than what is currently available and broadens the understanding of the symptom experience at end of life.

According to the Symptom Management Conceptual Model, which guided this inquiry (11), three domains (person, health/illness, and environment) affect and modify the three dimensions of the model (symptom experience, components of symptom management strategies, and outcomes). In this study, two domains are examined: person, and health/illness. The *person* domain that may influence the symptom experience includes individual characteristics such as age and sex. Characteristics from the *health/illness* domain include depressive symptomatology, site of cancer, and

ADL/IADL. Characteristics from the environment domain were not included in this

analysis as they were not present in the data sets. The outcome for this study was the

individual's perception of the presence of symptoms, a component of the *symptom*

experience dimension.

Data and Participants

This secondary data analysis employs pooled data from cancer patients who died

(N = 174) during one of three descriptive longitudinal studies. Inclusion criteria for all

studies required that the individuals have a diagnosis of cancer, be cognitively intact, and

be able to speak, read, and write English. Individuals under the care of a psychologist or

psychiatrist, or with a diagnosed emotional or psychological disorder, were excluded.

Specific inclusion criteria for *Rural Partnership Linkage For Cancer Care*

(CA56338, Rural study, N = 159) included patients over 21, undergoing treatment for a

solid tumor cancers, who resided in rural areas served by a National Cancer Institute

(NCI) designated Community Cancer Oncology Program (CCOP).

Specific inclusion criteria for *Family Home Care of Cancer – A Community-*

Based Model (NR01915, Community study, N = 1,150) were cancer patients newly

diagnosed with breast, colon, lung, or prostate cancer, who were 65 years of age or older.

For this study, participants were recruited from 24 community facilities in Michigan.

Specific inclusion criteria for *Family Home Care for Cancer Patients* (#PBR-32,

Cancer study, N = 192) were that patients between 20 and 80 years of age had at least one

dependency in an ADL or an IADL. Patients could be newly diagnosed or have recurring

cancer. Participants were recruited from 6 community-based cancer treatment centers

covering cities ranging in size from 20,000 to 500,000 and their surrounding rural areas in lower Michigan.

For all studies, nurse recruiters approached individuals who met the inclusion criteria, explained the studies, and obtained written consent. Data collection occurred by telephone and by mailed survey. The timing of the interviews varied by study and can be seen in Table 1.

Dates of death were confirmed by matching names, addresses, and social security numbers with death certificates obtained from the state Division of Vital Records. Dates of death were collected up to one year after the end of the study. Thus, the span of time from final interview to death could extend up to one year.

Measures

Symptoms were assessed using the self-report Symptom Experience Tool (14). Participants responded regarding the presence of 21 symptoms commonly experienced by individuals with cancer, indicating whether they experienced the symptom (= 1) or not (= 0).

Activities of daily living and instrumental activities of daily living were assessed using the modified index of ADL/IADL (15,16). Nine questions were asked regarding participants' independence (= 0) or dependence (= 1) with activities such as dressing, eating, walking, and transportation. A summary score was then created, with higher scores indicating more dependence in ADL/IADLs.

Depressive symptomatology was assessed using the Center for Epidemiologic Studies Depression (CES-D) measure, a 20-item assessment tool. Scoring of this instrument is on a 0 to 3 scale for each item, with the sum across the 20 items

representing the level of depressive symptomatology. Sums thus range from 0 to 60, with a score of 16 or higher representing clinically significant depressive symptomatology (17).

Time was coded in days from the last interview until death. Other information included age, sex, and site of cancer. The sites of cancer in participants consisted of lung, breast, colon, prostate, or other solid tumor cancers. For analysis, cancer sites were combined into two groups (*lung* and *other*), where *other* was the reference category.

Analysis

Preliminary analysis: Testing of assumptions

First, we examined a set of individuals who dropped out of the studies before completing the interview prior to death (n=38) to those who completed the final interview (n=136), using two-sample t-tests for continuous variables and X^2-tests for categorical variables, to determine if there were any discernable differences between the two groups. No significant differences in age, sex, site of cancer, depressive symptomatology, or ADL/IADLs were found. As no differences were found between groups, the missing at random assumption appears to be reasonable (18).

Second, we examined the assumptions of the Item Response Theory (IRT) Rasch model, including equal discrimination and the unidimensionality (19). In order to determine if symptoms were equally discriminating, a 2-parameter IRT model, which estimates discrimination as well as the difficulty of each symptom, was fit to the full sample (all individuals at all time points), as well as 4 sub-samples based on the time of the observation until death (0-99, 100-199, 200-299, and 300-400 days until death) using BILOG-MG. The fit of the 2-parameter model was compared to that of the 1-parameter

(Rasch) model using the Bayesian Information Criteria (BIC). In all five comparisons, the 1-parameter model had a smaller BIC value than the 2-parameter model, indicating that the 1-parameter model was a better fit. Note that for the purpose of the assumption testing, if symptom presence or absence was not indicated, it was assumed that the symptom was not present.

To examine the unidimensionality assumption, we looked at differential symptom functioning over time. First, a non-parametric approach was used by examining the ordering of symptoms due to their estimated difficulty in the Rasch model for the five samples mentioned above. Second, a parametric approach was used by comparing the fit of two HLM models: one model in which time was included in each equation at level 2, and another model in which time was included only in the intercept equation at level 2. No statistically significant difference between the two models was found ($X^2(df=20) = 24.00$; $p = 0.24$).

Hierarchical linear modeling analysis

The main analysis for this study embedded a one-parameter IRT (Rasch) model into a hierarchical linear model. A detailed description of how to set up an IRT Rasch model in an HLM framework has been discussed previously (20, 21, 23). Embedding IRT into an HLM framework produced several benefits, including the creation of a latent symptom experience variable, examination of the latent symptom experience trajectory and its relationship with covariates at the individual level, as well as handling the data on individuals who were missing one or more observations. Application of these analytic techniques advances our abilities to examine longitudinal symptom outcomes of individuals at the end of life.

Two models, unconditional and conditional, were estimated using HLM 6.21 (24). The unconditional model has 20 dummy variables for all but the reference symptom (fatigue) at level 1 and no covariates at level 2 or level 3, thereby yielding a readily interpretable ordering of symptoms as well as unadjusted symptom experience estimates for each person on each occasion that at least one symptom's presence or absence was recorded. The symptom experience over time is examined by testing linear and quadratic trajectories at level 2. To test the relationships between individual variables and symptom experience, these variables were incorporated into the model at level 3. In the final model, level 1 remains the same as in the unconditional model; however, a time-varying variable (days from interview until death) is added at level 2, and the time-invariant individual variables (age, sex, ADL/IADL at baseline, depressive symptomatology at baseline, site of cancer, and study) are added at level 3. To make the intercept more readily interpretable, age, depressive symptomatology, and dependency in ADL/IADL were centered on their corresponding grand means (70.79, 15.06, 2.31, respectively). Differences in study membership were controlled by creating dummy variables for each study and entering them in the model. The community study was used as the reference, as it had the greatest number of individuals who died.

<div align="center">Results</div>

Sample

Descriptive information on the 174 individuals who died during or within one year after completion of one of the three prospective, descriptive, longitudinal studies can be seen in Table 2 by study membership. Study participants were similar with respect to sex (overall 64% (n = 111) of the sample were male) and depressive symptomatology

distributions. Sixty-two percent of the sample had a diagnosis of lung cancer (n = 108).

Overall, individuals ranged in age from 38 to 91 years, with a mean of 71 years. There

were differences in study membership with respect to age, with the Rural study having a

greater age range and a lower mean age than the other two studies; this was in part due to

the inclusion criteria of the Community study being age 65 or older. ADL/IADLs were

significantly lower for the Cancer study participants compared to the Rural and

Community studies.

Of the 174 participants, 60 completed one interview, 70 completed two

interviews, 36 completed three interviews, and 8 completed all four interviews.

Participants' final interview prior to death ranged in time from two days to 365 days prior

to death, with a mean of 102 days (Figure 1). Thirty-four percent of the participant's last

interviews occurred within 60 days of death, and 12% occurred within 30 days of death.

Results of the unconditional model

The unconditional model described the symptom experience at end of life.

Fatigue, the most common symptom in the raw data, was used as the reference symptom.

The results of the unconditional model yield a readily interpretable ordering of

symptoms. Figure 2 shows the symptoms organized by their prevalence; the more

prevalent symptoms appear at the top (high values), while less prevalent symptoms

appear at the bottom (low values). Symptoms appearing close together in Figure 2 have

similar prevalence. The most prevalent symptom, fatigue, was followed by weakness,

then pain. The least prevalent symptom during the year before death among participants

was dehydration.

Results of the conditional model

Since our focus was to determine the symptom experience trajectory as well as its association with important individual variables (depressive symptomatology, ALD/IADLs, sex, site of cancer, and age), partial output for level 2 and 3 is reported in Table 3. Days from an interview until death ranged from 2 days to 365 days. Both the linear and quadratic trajectories were tested; however, the quadratic term did not significantly improve the model fit. Therefore, a linear trajectory was used in the final model. After controlling for other covariates, no significant difference was detected in symptom experience with proximity to death ($\hat{\gamma}_{010}$ = -0.076, p = 0.681).

After controlling for other covariates, significant differences in symptom experience by site of cancer were detected. Individuals with lung cancer experienced significantly higher symptom experience than individuals with other solid tumor cancers ($\hat{\gamma}_{003}$ = 0.411, p = 0.003). Thus, individuals with lung cancer experienced more symptoms in their last year of life than those who had other solid tumor cancers. Moreover, controlling for other covariates, there was a significant difference (p < 0.001) in symptom experience between participants who differed in depressive symptomatology at baseline. Higher depressive symptomatology at baseline was associated with greater symptom experience during the last year of life ($\hat{\gamma}_{006}$ = 0.047). Controlling for other covariates, dependency on ADL/IADL scales at baseline were found to be significantly associated with symptom experience (p = 0.022). In particular, individuals with higher levels of dependency at baseline tended to have worse symptom experience in the last year of their life ($\hat{\gamma}_{007}$ = 0.082). After controlling for other covariates, no significant

difference was detected in symptom experience between males and females ($\hat{\gamma}_{001}$ =

0.028, p = 0.808), nor was age found to be significantly associated with symptom

experience ($\hat{\gamma}_{002}$ = -0.005, p = 0.558).

Discussion

The purpose of this study was to describe the symptom experience at end of life

among individuals with cancer, and to determine if symptom experience differs with

proximity to death, depressive symptomatology, sex, site of cancer, or age, after

controlling for study membership. A contribution of this study is the successful

application of a new technique of analysis for longitudinal studies where symptom data

are collected. Additionally, as individuals of this analysis were recruited at the time of

diagnosis or during chemotherapy treatment, and had not been referred to hospice, this

research provides a view of the symptom experience at end of life among individuals

with cancer not previously well explored.

The five most prevalent symptoms in this population of cancer patients at end of

life were fatigue, weakness, pain, shortness of breath, and cough. Direct comparisons are

difficult to make with what has been reported in the extant literature describing

individuals with cancer in palliative care settings, due to differences in the symptom

assessment instruments used. However, Stromgren and colleagues (7), using the

European Organization for Research and Treatment of Cancer Quality-of-Life

Questionnaire (EORTC QLQ-C30), reported that among 176 individuals with advanced

cancer admitted into palliative care, the most prevalent symptom was fatigue, followed

by inactivity, and pain. This suggests that the symptoms experienced among individuals

with cancer who are not recruited from hospice and palliative care services may be comparable to those receiving hospice and palliative care.

Most extant longitudinal research has been conducted with individuals receiving hospice or palliative care and has assessed symptoms only in the last weeks or months before death (6, 25, 26, 27). These studies report that there was a worsening of symptom distress in the last month or weeks before death. The results of our study indicate that there was not a significant worsening of symptom experience as individuals with cancer approached the end of life. These results may appear counterintuitive at first glance, but may be due to two factors. First, studies used for this secondary data analysis had in common only the measure of the presence or absence of a symptom and did not have common measures of symptom severity or symptom distress. While symptoms may not be significantly increasing in prevalence at end of life, their severity or the distress may change as end-of-life approaches. Second, 12% of the interviews were conducted within one month of death. Since previous research has reported that changes in symptoms are seen only very close to death, there may not have been enough interviews or interviews were not frequent enough close to death to detect significant changes in symptom experience. Future research is needed among individuals with cancer, who are approaching end of life but not admitted to palliative care services, to ascertain if other symptom dimensions such as severity or distress along with more frequent symptom assessment may yield richer or different results.

Characteristics such as sex and age were not significantly associated with the overall end-of-life symptom experience. These results are contradictory to previous findings, which reported that being older or female were associated with higher symptom

prevalence for specific symptoms (12). The Symptom Management Conceptual Model states that person variables are intrinsic to the way an individual views and responds to the symptom experience; thus, only measuring symptom presence or absence may not have been adequate to assess how an individual views and responds to the symptom experience. Future research is needed to assess if, when additional dimensions of the symptom experience such as symptom severity or limitation are added, the person variables will be seen to impact the symptom experience in the last year of life.

In this study, health and illness variables included site of cancer, ADL/IADLs, and depressive symptomatology. As conceptualized by the Symptom Management Conceptual Model, health and illness variables had a direct effect on the symptom experience. Significant differences were seen between individuals with a diagnosis of lung cancer and those with other solid tumor cancers in the symptom experience. These findings further support previous findings by Donnelly and colleagues (28). Examining 37 symptoms among 1,000 individuals with advanced cancer admitted to palliative care services, they found significant differences in symptom prevalence between cancer sites. Thus, it is likely that health care providers will see differences in end-of-life symptom experience in individuals with different diagnoses.

Past work has demonstrated a relationship between symptoms and physical functioning (27, 29). Our findings extend this understanding of the relationship between symptoms and physical function at end of life. The finding that increased dependencies in physical functioning at initial assessment are associated with increased symptom experience further suggests that there is a reciprocal relationship between symptom experience and physical functioning which should be explored more fully.

Our results support and extend other research findings that suggest a strong relationship between depressive symptomatology and symptoms (30). This study extends previous findings on the relationship between depressive symptomatology and symptom experience to individuals with solid tumor cancers receiving chemotherapy near end of life, a group at high risk for worsening symptom experience. This study provides evidence that depressive symptomatology at the start of the study was associated with poorer symptom experience. Furthermore, individuals with high initial depressive symptomatology continued to report worse symptom experience than individuals with low depressive symptomatology as death approached. The participants of this study were recruited while receiving chemotherapy and not enrolled in hospice; however, we do not know whether or not they were told if they had a terminal prognosis. The knowledge of the terminal prognosis may have influenced depressive symptomatology in the participants. Future research is needed to clarify the directionality of the relationship between depression and symptoms in order to provide guidance to palliative care practitioners on how to improve the quality of life at the end of life for individuals with cancer.

Limitations

Although this analysis pooled 3 longitudinal descriptive studies, the sample size (N = 174) remains small. Increasing the sample size would allow greater differentiation between the various cancer diagnoses. Additionally, having a greater number and frequency of time points, especially closer to death, would allow for greater precision in the determination of the symptom experience trajectory.

Underestimation of the symptom experience at end of life may be present in this report, as those with the worst physical function deficits may not have enrolled in the studies or been able to respond to the interview closest to death. However, the potential response bias for those who did not respond to the interview closes to death can be viewed as minimal, since the 38 individuals who did not complete the interview prior to death were not significantly different in either personal or illness variables from those who did complete the interview prior to death.

As this was a secondary analysis of a data set, not all variables of interest that may influence symptom experience were available for analysis. Availability of additional covariates in the models tested (e.g., co-morbidities and stage of cancer) would enhance our understanding of symptom experience at end of life; however, those that were used are pertinent and further our understanding of the symptom experience at end of life among individuals with cancer not receiving hospice care.

Conclusions

This exploration extends our understanding of the symptom experience at end of life in several important ways. It examined a multiplicity of symptoms using data from three prospective studies. This previously unexplored sample consists of individuals with cancer in the last year of life who were receiving chemotherapy but not receiving hospice care. Thus, these findings allow us to be more confident about generalizing to the larger population of all cancer patients at end of life. Future research is needed to include greater detail in the symptom experience dimension, such as the assessment of symptom severity. With greater understanding of the symptom experience, intervention strategies

reflected in the model as the domain of symptom management can be targeted to achieve

the desired outcome of increased quality of life at end of life.

ACKNOWLEDGEMENTS

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Table 1. Timing of Interview Data by Study

Study	Baseline interview or date of diagnosis of cancer	2 months	3 months	4 months	6 months	9 months	12 months
Cancer study			x		x	x	x
Community study		x		x	x		x
Rural study*	x		x		x	x	

* Rural study recruitment was not at diagnosis of cancer

Table 2. Descriptive Characteristics at Entry into Study

	Rural study N = 27		Community study N = 112		Cancer study N = 34	
	Min - Max	Mean (SD)	Min - Max	Mean (SD)	Min - Max	Mean (SD)
Age	38 - 82	62.6 (11.7)*	65-91	72.6 (5.63)	62-91	71.1 (6.66)
Depressive symptomatology	1 - 37	15.3 (8.10)	0-37	14.9 (7.93)	2-35	15.6 (9.13)
ADL/IADL	0 - 7	2.6 (2.31)	0-8	2.4 (2.15)	0-5	1.5 (1.68)*
	N	%	N	%	N	%
Sex						
Male	16	59%	73	65%	22	65%
Female	11	41%	39	35%	12	35%
Site of cancer						
Breast	3	11%	2	2%	1	3%
Colon	5	19%	15	13%	1	3%
Lung	10	37%	87	78%	11	32%
Prostate	1	4%	8	7%	2	6%
Other cancers	8	30%	0	0%	11	32%

* p < 0.05 difference compared with other studies

Table 3. Partial Output of Estimates for the Conditional Model (Excluding Symptoms'

Prevalence)

Variable	Coefficient	Standard Error	P value
Intercept, γ_{000}	1.199	0.194	< 0.001
Female, γ_{001}	0.028	0.117	0.808
Age, γ_{002}	-0.005	0.009	0.558
Lung, γ_{003}	0.411	0.132	0.003
Rural study, γ_{004}	0.318	0.204	0.121
Cancer study, γ_{005}	-0.308	0.163	0.061
Depressive symptomatology, γ_{006}	0.047	0.007	<0.001
Dependencies in ADL/IADL, γ_{007}	0.082	0.035	0.022
Proximity to death, γ_{010}	-0.076	0.184	0.681

Mean = -101.86
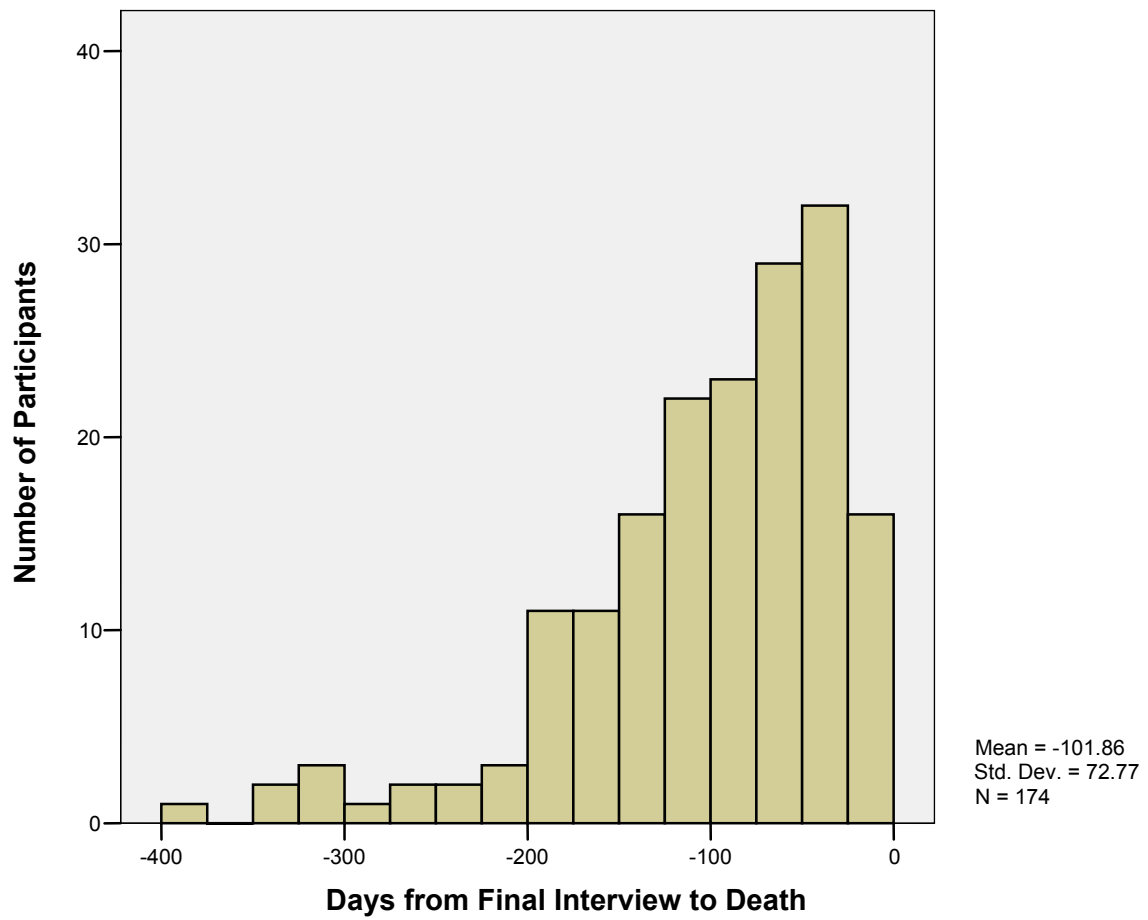Std. Dev. = 72.77
N = 174
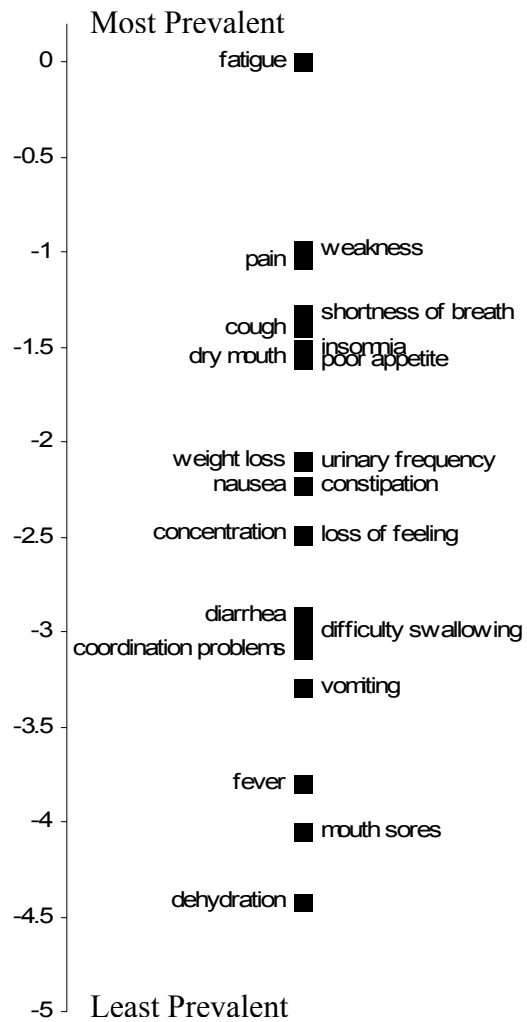
Figure 1. Histogram for the day of last interview prior to death

Figure 2. Symptom prevalences according to the unconditional model.